DETERMINING PROFILES OF RISK FOR SEXUALLY TRANSMITTED INFECTIONS IN YOUNG ADULTS

A Dissertation

by

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ABSTRACT

Sexually transmitted infections (STI) disproportionately affect adolescents, young adults, women and racial/ethnic minorities, leading to significant reproductive morbidities. Young minority women in the US are also at increased risk for unintended pregnancies, which coupled with STIs, can lead to serious complications in mothers and infants. Prevention of STIs in young minority women is greatly needed in order to improve reproductive and pregnancy health. However, interventions to reduce STIs in young minority women have had limited effectiveness. Furthermore, screening young women for chlamydia and gonorrhea is recommended but uptake is suboptimal.

Syndemic theory hypothesizes that diseases co-occur and interact with other social afflictions to increase the risk of STIs. However, population-based studies on STI syndemics have not been conducted and statistical techniques are limited in determining how risk factors interact. In pregnant women, associations between STIs and perinatal outcomes are inconsistent but few studies have examined the effect of maternal factors such as age in adverse outcomes. This dissertation examined two statistical approaches to measure syndemics in a nationally representative sample of US young adults, and determined sex and race/ethnic specific profiles for STI risk. This dissertation also determined if perinatal outcomes following STIs are influenced by maternal age in minority women.

The first study compared composite scoring and latent class analysis (LCA) to identify syndemic profiles in men and women using the National Health and Nutrition

Examination Survey from 2011-2014. LCA identified different STI risk profiles that composite scoring alone could not. Women with increased odds of STI (AOR: 2.19 CI 95% 1.2-3.8) exhibited a syndemic of depression, substance use and sexual risk behaviors that composite scoring was unable to uncover. The second study, using the same dataset, applied LCA to determine race/ethnic specific STI risk profiles. Interestingly, Black females displayed more co-occurring risk factors (syndemic), despite lower sexual behavior risks compared to other women. The third study, examined a population of primarily minority pregnant women to determine if associations between *Chlamydia trachomatis* and perinatal outcomes are influenced by maternal age (a factor that influences screening). In young women (age <25), chlamydia was associated with medically indicated preterm birth (RRadj=2.25 95% CI 1.35-3.77). In older women (age $\geq$ 25), no associations with preterm birth subtypes were found, but *C. trachomatis* was marginally associated with term preeclampsia (RRadj=1.49 CI 95% 0.91-2.45). Further stratifications by race/ethnicity revealed an increased risk in chlamydia associated medically indicated preterm birth among white women, and preeclampsia among Black women.

Modeling syndemics by sex and race identified risk profiles that can be utilized to develop culturally competent, targeted interventions to reduce STIs among minorities. Findings from the prenatal study suggest maternal age could influence outcomes following infection that may inform prenatal STI screening recommendations.

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NOMENCLATURE

STI	Sexually Transmitted Infections
HIV	Human Immunodeficiency Virus
HSV-2	Herpes Simplex Virus – type 2
HPV	Human Papillomavirus
MSM	Men who have sex with men
CDC	Centers for Disease Control and Prevention
ACOG	American College of Obstetricians and Gynecologists
USPSTF	United States Preventive Services Task Force
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
PHQ-9	Patient Health Questionnaire – 9
ACASI	Audio Computer Assisted Self-Interview
DUQ	Drug Use Questionnaire
OR	Odds Ratio
AOR	Adjusted Odds Ratio
RR	Relative Risk
PR	Prevalence Ratio
CI	Confidence Interval
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

1. INTRODUCTION

1.1. Sexually Transmitted Infections

Sexually transmitted infections (STIs) are a significant public health concern, as they are increasingly prevalent in the United States and can lead to permanent reproductive damage and increased transmission of human immunodeficiency virus (HIV) [1]. STIs include a myriad of bacterial and viral infections, such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, syphilis, *Trichomonas vaginalis*, herpes simplex virus (HSV) and human papillomavirus (HPV), and are transmitted primarily through vaginal, anal and oral sex [1]. In 2017 there were over two million cases of chlamydia, gonorrhea and syphilis reported to the Centers for Disease Control (CDC) [2]. The prevalence of chlamydia was 528 per 100,000, gonorrhea was 171.9 per 100,000 and syphilis was 9.5 per 100,000 [3]. To put this in perspective, from 2013-2017 there was a 67% increase in gonorrhea and 76% increase in syphilis. A total of 1.7 million cases of chlamydia were observed in the same year, making it the most reported disease to the CDC.

Most concerning is that reportable STIs only represent a fraction of the true burden of disease [4]. Although several STIs such as chlamydia, gonorrhea, syphilis and trichomoniasis can be cured through antibiotic treatment [5], an estimated 61-88% of chlamydia cases are asymptomatic [6]. Similarly, 85% of trichomoniasis [7 8], 50% of gonorrhea [8], and an estimated 20-30% syphilis cases in the United States are asymptomatic [9]. Thus, many individuals go untreated further increasing their risk of

significant reproductive complications [10 11]. Additionally, there is a significant concern over antibiotic resistant strains of gonorrhea [12 13].

1.2. Age Specific Prevalence

Adolescence and young adulthood (ages 15-24) are important periods for the development of intimate relationships [1], coping mechanisms such as alcohol and drug use [14], and STI risk behaviors [15]. This age group represents only 25% of the sexually active population, but accounts for half of all new reportable STIs in the United States [1]. In an assessment of STI prevalence from a nationally representative sample of men and women from 1999-2008, chlamydia prevalence was estimated at 3.2% (CI 95% 2.26%-4.52%) in women aged 15-24 and 1.66% (CI 95% 1.07%-2.55%) in men of the same age [8]. Gonorrhea prevalence was 0.62% (CI 95% 0.38%-1.03%) in women and 0.32% (CI 95% 0.12%-0.84%) in men aged 15-24 [8]. Trichomoniasis prevalence was an estimated 1.50% (CI 0.91%-2.44%) in women and the prevalence ratio was 1.64 (CI 95% 1.25-2.15) among men age 15-24 [8].

Multiple factors may influence the higher prevalence of STIs among adolescents and young adults, including the introduction of mental health challenges [16], substance and alcohol use [17 18] and cultural or social factors [15 19]. For example, in a cross sectional analysis of Project STYLE data collected between 2004-2007 from three site (Chicago, IL, Atlanta, GA, and Providence, RI) examining 840 adolescents evaluated for psychiatric disorders, the odds of risky sexual behaviors and STI positivity was higher among those with a diagnosed mental illness than individuals not meeting the criteria for mental illness [16]. A subset of 750 girls aged 16-18 from The Pittsburgh Girls Study, a

community-wide longitudinal study in Pittsburgh, PA beginning in 2000, found that depression in 16 year old girls was predictive of any self-reported STI diagnosis (e.g., gonorrhea, chlamydia, herpes, HIV, genital warts) [20]. Sexual risk behavior was associated with self-reported STI in 17 year old girls, and greater alcohol use was predictive of self-reported STI in 18 year old girls, where frequency of alcohol use mediated the association in older girls [20].

While most young people initiate healthy sexual relationships, others engage in health risk behaviors such as condomless sex and sex with multiple partners [15]. For instance, while condoms remain the most popular form of contraception among adolescents, students from the Youth Risk Behavior Surveillance Survey reported roughly 57% used condoms at their last intercourse and 11% reported more than five sexual partners in their lifetime [14 21]. Further, in a longitudinal analysis of adolescents from Monitoring the Future from 1991-2015, 20% of 18 year old's reported frequent binge drinking compared to less than 5% of 13-14 year old's [22]. And up to 60% of adolescents try or use illicit drugs by age 14 [15]. Alcohol and drug use impair judgment and may lead to risky sexual behaviors and increased risk of STIs [23].

1.3. Disparities in Infection by Gender

While young males and females are both at risk for STIs, young women are disproportionately affected by these pathogens [3]. The prevalence of chlamydia in women (2.0, CI 95% 1.5-2.5) was higher than men (1.4, CI 95% 1.1-1.8) from a longitudinal analysis of nationally representative individuals age 14-39 [11]. It is estimated that one in four sexually active young women have an STI [1]. Biologically, young women and girls

may be at higher risk of contracting STIs due to cervical ectopy. This is where the columnar epithelium of the ectocervix extends to the proximal portion of the cervix leading to a thin vascular layer that is easily permeated by pathogens [24]. As a result, STIs are of particular concern for young women. For example, chlamydia and gonorrhea can lead to pelvic inflammatory disease and subsequent ectopic pregnancy, chronic pelvic pain or infertility [4 25]. Untreated syphilis can cause neurological complications including altered behavior, paralysis, dementia, and even blindness [26 27].

STIs are often asymptomatic for both men and women, but in young women (e.g. up to 80% of *C. trachomatis* cases are asymptomatic in women vs. 60% in males) may more frequently go untreated [6]. In fact, due to their asymptomatic nature, screening for *Chlamydia trachomatis* and *N. gonorrhoeae* is recommended for women younger than 25 years old to reduce reproductive complications in the population [5 28]. Unfortunately, screening uptake is poor [29]. Risk of STIs in this group is also influenced by women's social and political standing in society, the availability of reproductive health services, violence perpetrated against women, and misinformation regarding contraception usage [30 31]. These are serious concerns as many STIs lead to more serious long-term consequence in women than men [32]. For example, *C. trachomatis* and *N. gonorrhoeae* can lead to pelvic inflammatory disease and subsequent long-term complications such as infertility [10 25], and HPV in women can lead to cervical cancer [33 34]. Thus, further investigation into the particular STI prevention needs of women and girls should be a public health priority.

1.4. Racial/Ethnic Disparities

Racial/ethnic disparities are immensely evident in STI and HIV rates. From 2010-2014, Blacks accounted for just under half (45%) of all reported HIV infections in the United States [3 35]. Black women (5.2, CI 95% 4.0-6.4) had five times the rate of chlamydia and Hispanic women (2.3, CI 95% 1.4-3.1) two times the rate as white women [11]. Approximately 37% of all syphilis cases in 2016 were among Black individuals, with Black women having seven times the rate of white women [36]. Syphilis among pregnant women is also a particular concern due to the increasing rates (153% increase from 2013-2017) of congenital syphilis [3 37]. Black women accounted for 58.9 per 100,000 of congenital syphilis cases in 2016 compared to 9.7 per 100,000 in white women [3 37]. Disparities are similar among men, with Black men disproportionately affected by STIs when compared to white men [38-40]. A longitudinal study that included 1,880 males aged 19-29 revealed that Black males had 4 times the odds of *C. trachomatis* compared to white males [40].

Black men and women are both consistently at increased odds of STIs when compared to their white counterparts, along with Hispanic men and women. Data from waves III and IV of National Longitudinal Study of Adolescent Health (Add Health) were examined to determine the population based estimates of STI risk in 11,045 young adults age 18-34 [39]. Black (OR=2.5, CI 95% 1.9-3.0) and gay Black men (OR=5.4, CI 95% 4.1-6.8) had significantly higher STIs compared to white men. Similarly, Black women (OR=1.3, CI 95% 0.9-1.7) and Black gay women (OR=11.6 CI 95% 3.0-20.1) had increased rates of STIs (e.g., chlamydia, gonorrhea, syphilis) or HIV compared to

white women [39]. Data from 27 US states between 2005-2008, shows that Hispanic men have 3 times the rate of primary and secondary syphilis compared to white men [41]. Among 51,464 women diagnosed with chlamydia from 1992-2014 in King County, WA, the risk for Hispanic women was 32% [42]. Although racial/ethnic groups at high risk for STIs are well established, interventions that exclude social determinants of health and health equity and focus only on behavioral interventions to reduce STI rates have had limited effectiveness [43-45]. Programs created without considering the contextual and socio-ecological influences on STI risk may not be sufficient to observe a widespread reduction of STI rates [46].

1.5. Complications related to STIs during Pregnancy

Prenatal acquisition of STIs are concerning if left untreated as infections may transmit from mother to infant during pregnancy, and result in significant pregnancy and delivery complications. For instance, the incidence of congenital syphilis has increased dramatically over the past five years from 8.4 to 11.6 cases per 100,000 [4 37]. Similarly, Chlamydia has been associated with adverse birth outcomes including preterm birth, preterm premature rupture of membranes (PROM), and preeclampsia among others [10 47-49]. Coinfection with any STI significantly increases the risk of HIV infection [4 50 51]. Young women are at increased risk of unintended pregnancy and prenatal STIs [52 53], which are associated with adverse pregnancy outcomes [48 49].

There are discrepancies in the association between chlamydia and specific adverse pregnancy outcomes, the reasons for which are not well understood. Preterm birth [48 54], stillbirth [55 56], and preeclampsia related preterm birth [57 58] have all been linked

to chlamydia infection during pregnancy. Inconsistency in the findings from prenatal studies may be due to inconsistent definitions of the outcomes (e.g. preterm birth classifications), differences in the study designs, and lack of studies within large cohorts of high risk pregnant women. Furthermore, studies have not examined factors such as race and maternal age that may modify the risk of pregnancy outcomes following prenatal *C. trachomatis* [59]. Providing support for specific adverse outcomes will be useful to determining effective screening recommendations for prenatal populations at high risk for infection.

1.6. Assessing Multiple Risk Factors: A Syndemic Approach

Traditional STI prevention programs focus on individual behaviors, but have not typically included sociological perspectives to health vulnerabilities and the needs of socially disadvantaged groups [43 46]. While sexual behaviors such as condomless anal and vaginal sex are well-known risk factors for STIs [60 61], reporting of those behaviors vary by gender and race/ethnicity among adolescents and young adults [62]. Thus, aiming to modify certain sexual behaviors may not be effective for all groups [44]. For example, 48.6% (95% CI 44.5%-52.7%) of males aged 14-19 reported two or more sex partners in the past year, compared to 39.4% (95% CI 35.5%-43.4%) of females aged 14-19 [60]. In a longitudinal study of 13,998 adolescents from the Add Health, Black girls were least likely to report varied high-risk sexual behaviors, but are consistently more likely to test positive for STIs compared to non-Hispanic white girls [61]. In another longitudinal study of 7015 adolescent girls from Add Health, Non-Hispanic white girls report engaging in anal and oral sex and had an earlier sexual debut, but had fewer high risk partners

compared to other race/ethnicities [62]. Hispanic girls reported low rates of condom use and fewer partners, but had partners at higher risk for STIs, while Black girls reported low rates of oral and anal sex with high rates of condom use, but had the most sexual partners with increased STI risk [62]. Risk behaviors may *interact* differently as a function of race/ethnicity and gender [46 61]. Therefore, it is recommended that future interventions focus on multiple behaviors, and psychosocial risks to effectively reduce STIs [19 63].

Syndemic theory may be applied to STI research to improve current prevention efforts [64]. *Syndemic theory suggests that diseases do not exist in isolation, but that multiple risk factors [64] or disease conditions [65] and the individuals social environment co-occur and interact to influence the course and outcome of disease [66].* The exacerbation of harmful social conditions can then compound health problems [67]. Additionally, experiences of discrimination cluster health problems, intensifying how social systems such as racism and sexism reinforce specific challenges that perpetuate epidemics within certain populations [68 69]. Individuals at the intersection of syndemic factors seem to focus mainly on short term pleasure and have limited expectations of a future [70]. Social disparities in these contexts create an environment where high-risk behaviors may be more acceptable. Syndemic approaches encourage exploration of social institutions and environments that create risk and simultaneously produce disparities in disease outcomes in specific populations. Syndemics addresses the "failure to examine linked phenomena" while maintaining independence from simultaneously occurring risk factors [69]. Applying a syndemic framework to STI prevention may be vital

to advancing the development of culturally appropriate and targeted interventions to reduce disease among disparate populations [66 71 72].

The syndemic framework was first used to understand the marginalized experiences of the HIV epidemic and how substance use, intimate partner and social violence were interrelated to increase HIV risk among men who have sex with men (MSM) [73-75]. A cross-sectional evaluation of 158 women living in a Connecticut community found that experiences with drug and alcohol use, depression, and post-traumatic stress from previous intimate partner violence signified a syndemic that reduced the individuals capacity to negotiate condom use with partners [76]. Syndemics socially shape the distribution of disease and present a biologic synergism at the individual level [69]. Social impact factors such as violence indicators are associated with increased risk of STI, along with housing insecurity, childhood physical abuse, and depression [77]. Coulter et al. performed a cross-sectional evaluation of 467 sexual minority women ages 18-24 using a structural equations model and determined that syndemics were associated with discrimination related to sexual orientation [68]. In another cross-sectional evaluation of 151 adolescents and young adults ages 15-24 recruited from the Transgender Young Project, results indicated that low self-esteem, polysubstance use, and intimate partner violence were indicators of a syndemic associated with increased risk of HIV [78]. These findings were further confirmed by Chakrapani and colleagues who evaluated 600 MSM and transgender women in India and reported a dose-response effect for increasing syndemic conditions and HIV risk [79].

Syndemics for many marginalized populations included alcohol abuse, drug use, depressive symptoms, and risky sexual behaviors [73-75].

Studies of syndemics in HIV are primarily amongst MSM [80-82] and sexual minorities [76 78]. Furthermore, these studies focused on indicators of substance use and violence [83]. Examinations of syndemics among women in the context of HIV risk have also been conducted [75 84 85]. Women consistently have higher syndemic burdens compared to men in relation to HIV risk and subsequent infection due to societal disadvantage, particularly women of color [86]. Although syndemics are well examined in the HIV literature, other STIs and young adult populations have been relatively overlooked. One study of 199 Canadian adolescent women ages 13-17 determined that a syndemic of depression, substance use and sexual risk taking was associated with any STI risk [87]. Another longitudinal study of 125 young adult Mexican-American women determined that the prevalence of HSV-2 was 56.8%, and a syndemic of co-occurring genital herpes, injection heroin use, Hepatitis C, previous sexual violence, incarceration, and mental illness was determined [88]. No other studies of this kind have been conducted in this population.

Future examinations of syndemics in STIs should explore the extent to which risks interact to increase disease susceptibility or progression. Literature does not well document how multiple psychosocial problems contribute to the increased risk of STIs from syndemics [67 89 90]. Additionally, studies have overwhelmingly quantified syndemics through the use of composite scoring methods [91-93]. This approach assigns values to social conditions that are translated into a syndemic score that subsequently

summarizes the number of problems reported by each participant. Higher scores from the count summaries are interpreted as a greater syndemic interaction [90]. Composite syndemic score methods were introduced to form baseline tests for interactions, not to determine the presence of syndemics, indicating that majority of syndemics literature are not using statistically comprehensive approaches to quantify the problem [70]. Composite syndemic score methods may not produce estimates with clear implications for public health interventions or policies, test for interactions or identify synergies [90].

1.7. Dissertation Aims

This dissertation aims to improve scientific knowledge through *identifying syndemic profiles for STI's among young adults in the context of ecological perspectives and subsequently examining risk one prevalent STI and related outcomes in pregnancy*. A prevalent STI, chlamydia, will be examined in a pregnancy cohort to determine associated pregnancy outcomes after infection. This is important due to the high prevalence of chlamydia in the population and the long-term effects of asymptomatic and untreated chlamydia on women's reproductive health. Next, a syndemic theoretical framework is proposed that includes social, behavioral, and mental health factors that may contribute to the increased risk of STIs among young adults. This goes beyond understanding the prevalence of STIs in this population to identifying specific risk factors that co-occur to increase risk. These studies are expected to result in gender and racial specific profiles of STI risk that may be further expanded to directly inform prevention activities. This innovative approach will include previously neglected gaps in STI research. The specific aims include:

1. To examine risk factors that may increase the odds of prenatal chlamydia and associated pregnancy outcomes among minority women.
2. To compare multiple methods to quantify STI syndemics within a nationally representative sample of young adults.
3. To determine if syndemics increase the odds for STIs in young adults by gender and race/ethnicity.

The results obtained in these studies may be used to make informed recommendations for STI prevention programs targeting young adults, specifically by gender and race/ethnicity. Findings from these studies will improve the knowledge and understanding of specific pathways that influence racial and ethnic disparities for STIs in the United States.

2. UNDERSTANDING FACTORS RELATED TO PRENATAL *CHLAMYDIA TRACHOMATIS* AND ASSOCIATED PERINATAL OUTCOMES

2.1. Introduction

According to Centers for Disease Control (CDC), in 2016 there were 1.59 million cases of chlamydia in the U.S., a 4.7% increase since 2015 [94]. *Chlamydia trachomatis* is a prevalent and predominantly asymptomatic bacterial sexually transmitted infection (STI) that increases the risk of pelvic inflammatory disease, causing infertility and ectopic pregnancy [95]. *C. trachomatis* during pregnancy can lead to poor maternal and infant outcomes [96]. However, associations between *C. trachomatis* and specific adverse outcomes are largely conflicting [49 55 97]. Unfortunately, some minority populations remain underrepresented in studies of prenatal *C. trachomatis* and its effects on pregnancy outcomes.

The reasons for the discrepant findings in studies of prenatal *C. trachomatis* and pregnancy outcomes are not clear. Preterm birth (delivery <37 weeks of gestation) has been extensively studied [56 98 99]. *C. trachomatis* was associated with preterm premature rupture of membranes (PROM) and preterm delivery in a population-based retrospective cohort study of infant birth certificates from 851 pregnant women in Washington state [49]. In a retrospective cohort study of 357,217 women residing in Australia between 1999-2008, *C. trachomatis* infection was marginally associated with stillbirth but not preterm birth [55]. A study of 194,045 pregnancies found reduced odds of preterm birth [98]. Evidence suggests that *C. trachomatis* is also linked to preeclampsia; a maternal hypertensive disorder that can lead to medically indicated preterm birth in up to 20-30%

of cases [57].Others have found no associations between *C. trachomatis* and perinatal outcomes [99 100]. Inconsistent findings linking *C. trachomatis* to a specific adverse pregnancy outcome(s) may be due to different outcome definitions, inclusion of heterogeneous populations and differences in study design. Furthermore, adverse pregnancy outcomes such as preterm birth and preeclampsia have several subtypes with various etiologies that can impact the results of studies.

The prevalence of chlamydia is much higher in young women than older women, which mimics the STI screening recommendations for pregnant women outlined by the US Preventative Services Task Force (USPSTF) and the CDC [5 101]. The CDC recommends screening for all pregnant women, and the USPSTF suggest screening for pregnant women at high risk (e.g. history of STI, young age, history of sex work) for STIs. In 2015, the CDC changed prenatal *C. trachomatis* screening recommendations from all pregnant women to pregnant women less than 25 years old or women at increased risk of developing an STI [101]. Tao et al. suggest that differences in screening recommendations may be resulting in unreliable data that focuses on women in higher risk categories [59]. Chlamydia screening is based on the assumption that the probability of adverse outcomes is only dependent on population chlamydia prevalence [59]. However, as Tao et al point out, if maternal age modifies the risk of adverse outcomes in chlamydia positive women, then the probability of those adverse outcomes will rely on both chlamydia prevalence and maternal age [59]. These findings supported increased testing among younger women as supported by the increased prevalence among this population, but suggested more investigation into age specific chlamydia related adverse

pregnancy outcomes was necessary. However, Tao et al., points out that it is unclear if factors such as race and maternal age modify the risk of pregnancy outcomes following prenatal *C. trachomatis* [59]. Young maternal age, race and ethnicity are known risk factors for *C. trachomatis* infection during pregnancy [102], but both young and advanced maternal age are associated with adverse pregnancy outcomes. Race and ethnicity are also well-known risk factor for several maternal and fetal complications [102]. Furthermore, it is unknown if a woman with young maternal age have the same, lower, or higher risk of adverse pregnancy outcomes following infection compared to older women. Coupled with inconsistencies in identifying a specific adverse outcome related to prenatal chlamydia, further research in this area is needed.

The objective of this study was to determine if prenatal *C. trachomatis* is associated with medically indicated preterm birth or spontaneous preterm birth in a large population of pregnant women. Additionally, since preeclampsia is a well-known indicator for preterm birth (~ 40% of medically indicated preterm births are due to preeclampsia) and has been linked to *C. trachomatis* infection [57], we examined associations between prenatal chlamydia and preeclampsia with and without a preterm delivery.

2.2. Methods

Data from the PeriBank repository was used in this retrospective cohort study [103]. Briefly, women in PeriBank delivered at area hospitals in Houston, TX and were recruited by trained study personnel who approach eligible gravidae at the time of their admission to labor and delivery. After informed consent was obtained, over 4,700

variables of clinical information were directly extracted from electronic medical records and accompanying prenatal records. Charts were routinely audited by a board certified maternal-fetal medicine physician scientist to ensure quality of the data. PeriBank was approved by the Institutional Review Board at Texas Children's Hospital and Baylor College of Medicine. The current study included participants with records cataloged in the PeriBank system from 2011-2017. Our analysis included 22,772 singleton pregnancies that had a confirmed prenatal *C. trachomatis* diagnostic test performed (100%). This study was approved by the Texas A&M University Institutional Review Board.

2.2.1. Data Collection

All laboratory information was abstracted from medical records. Provider collected vaginal swab and blood specimens were collected at first prenatal visit, processed and stored by clinical personnel trained in microbiology, pathology, and perinatal surgical expertise under uniformed protocol. Vaginal epithelial cell samples were collected and nucleic acid amplification tests (NAATs) and were performed as recommended by the American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control (CDC) to detect *C. trachomatis* and *Neisseria gonorrhoeae* [104 105]. Other genital infections included in the database were HIV, syphilis, bacterial vaginosis, hepatitis B, and genital herpes simplex virus (HSV)-2. Laboratory confirmed results were queried from the PeriBank database and extracted for analysis.

2.2.2. Outcome

Preterm birth was defined as delivery less than 37 weeks gestation determine by self-reported last menstrual period and confirmed with ultrasound. Ultrasound was used to mediate any discrepancies with last menstrual period. Subtypes of preterm birth were extracted from the patient medical record and classified as spontaneous or medically indicated. Spontaneous preterm births were defined as births from spontaneous labor or preterm premature rupture of membranes, while medically indicated preterm birth was classified as any maternal or fetal distress that resulted in medical intervention leading to delivery prior to 37 weeks. Due to the infrequency of preterm premature rupture of membranes (PROM) recorded in the medical records (0.10%), the variable was not included as an independent outcome.

2.2.3. Maternal Characteristics

Information was collected on maternal demographic characteristics, previous pregnancy complications, historical conditions, and fetal outcomes. Variables included maternal age, race, country of birth, marital status, education, income and insurance type. Smoking, drug and alcohol use were asked at the time of triage for the past year and included in the model. Previous pregnancy information of interest were gravida and parity, comorbidities (i.e. congenital heart defects, hypothyroidism, diabetes, preeclampsia, hypertension, or seizure disorders), and previous pregnancy or birth complications. Biometric measures of body mass index (BMI), blood pressure, height and weight were also collected. Current pregnancy information included gestational age (GA) at first prenatal visit, whether the birth was live or stillbirth, vaginal or cesarean

birth, the infant sex, chorioamnionitis, preeclampsia or normal blood pressure (normotensive).

2.2.4. Statistical Analysis

Modified Poisson regression [106] with robust error measurements was used to estimate relative risk (RR) and 95% confidence intervals (CI) for all analyses. It is well known that odds ratios are often used to approximate relative risk (RR) or prevalence ratios (PR) but often lead to overestimations for non-rare events [106]. There are several methods well described in the epidemiologic literature to directly calculate RR or PR rather than relying on OR to estimate risk. Two common methods are log-binomial logistic regression and modified Poisson regression with robust (generalized estimating equations (GEE) or "sandwich") variance estimates (used for binary data) [107]. Log-binomial regression was initially used however, this method is less numerically stable and there were issues with convergence. A limitation of Poisson are conservative confidence limits and overestimates of binomial errors. However, the sandwich variance estimate (i.e. the modified version) avoids the conservative confidence intervals and produces similar estimates to other approaches. This approach has been validated in SAS using the GENMOD procedure with the REPEATED ESTIMATES statement and is an accepted and appropriate method for this data [108].

Univariate analysis examined associations between demographic and clinical variables and *C. trachomatis* infection. PR and 95% confidence intervals (CI) are reported. Known risk factors for chlamydia were included in the models to control for confounding [8]. Howards et al. suggests that some previous pregnancy variables (e.g.

previous preterm birth) may not need to be adjusted for in perinatal studies estimating the effect of an exposure on an outcome [109]. Specifically, the effect of a previous preterm birth on a subsequent preterm birth is heavily influence by the gestational age of that previous birth [54], which was not available in this study. Therefore, previous preterm birth was not adjusted for in this analysis. Multivariable analyses were used to examine associations between *C. trachomatis* and adverse birth outcomes. Model 1 included no adjustments for covariates and examined the crude association between *C. trachomatis* and preterm birth subtypes. Model 2 included adjustments for maternal age, race/ethnicity and foreign born status (where necessary), marital status, education, insurance type, alcohol use, and gestational age at first prenatal visit. Model 3 included adjustments in model 2 in addition to a composite STI variable (HIV, *Neisseria gonorrhoeae*, bacterial vaginosis, group B streptococcus and syphilis) to consider confounding related to co-infections, and any reported maternal comorbidities as indicated in the patient medical record. The variable HSV-2 was not included in the model 3 adjustments due to the high number of missing, although significantly associated with chlamydia positivity. Lower urinary tract infection was also excluded in model 3 due to its low prevalence in the sample. Further analysis was conducted stratified by age less than 25 and greater than or equal to 25 and by race/ethnicity. All analysis were conducted in SAS V9.4 (Cary, NC).

2.3. Results

2.3.1. Descriptive results

Women in the study were majority older than 25 years (frequency 70.7%, 95%

CI 0.70-0.71), Hispanic (62.5%, 95% CI 0.62-0.63), foreign-born (61.6%, 95% CI 0.61-0.62), married (64.0%, 95%CI 0.64-0.65), and were Medicaid or CHIP recipients (67.1%, 95% CI 0.67-0.68). Prevalence of *C. trachomatis* was 4.3% and was the most frequently diagnosed STI. Trends for chlamydia increased from 2011-2015 then decreased over the remaining years with younger women having a higher prevalence. Prenatal *C. trachomatis* was significantly associated with younger age (PR=3.5, 95% CI 3.1-4.0), black race (PR=4.3, 95% CI 3.2-5.8), Hispanic ethnicity (PR=2.1, 95% CI 1.4-3.2) being unmarried (PR=3.05 95% CI 3.1-4.0), being less educated (High school graduate PR=5.0, 95% CI 3.2-8.0) and having no insurance (PR=5.4, CI 95% 3.7-7.7) (**Table 2.1**). Cesarean deliveries were lower among women with *C. trachomatis* (PR=0.81, 95% CI 0.70-0.93). Women who had their first prenatal visit in the third trimester were more likely to have *C. trachomatis* infection (PR=1.77, 95% CI 1.3-2.4) than women who received prenatal care in the first trimester, however most women engaged in prenatal care in their first trimester (n=11040, 56%).

The overall prevalence of preterm birth was 9.4%. Spontaneous preterm birth (3.6%, 95%CI 0.03-0.04) was the most commonly reported subtype, followed by medically indicated (3.4%, 95% CI 0.03-0.04). Preeclampsia prevalence was 7% (n=1467) in the population. Of those preeclampsia cases, half were preterm preeclampsia (n=741) and about half were term preeclampsia (n=726).

Table 2.1. Maternal characteristics and prevalence rates by C. trachomatis status N=22,772.

Variable	Chlamydia negative n (%)	Chlamydia positive n (%)	PR	95% CI
Demographics				
Maternal age				
35> (ref)	4627 (213%)	73 (7.5%)	--	--
25-34	12040 (55.3%)	378 (38.7%)	**1.96**	**1.53-2.51**
<25	5094 (23.4%)	525 (53.8%)	**3.84**	**2.34-6.31**
Race				
NH White (ref)	3914 (18.0 %)	45 (4.6%)	--	--
NH Black	2770 (12.7%)	201 (20.6%)	**4.29**	**3.18-5.79**
Hispanic	13520 (62.1%)	693 (70.9%)	**2.07**	**1.35-3.17**
Other*	1566 (7.2%)	38 (3.9%)	--	--
Country of birth				
US-born (ref)	7795 (38.2%)	390 (42.2%)	--	--
Foreign born	12585 (61.7%)	533 (57.7%)	**0.85**	**0.75-0.97**
Marital status				
Married (ref)	13849 (65.3%)	344 (35.8%)	--	--
Unmarried	7369 (34.7%)	617 (64.2%)	**3.05**	**3.09-3.96**
Education				
College (ref)	5543 (29.7%)	56 (6.6%)	--	--
Some College	1999 (10.7%)	118 (13.9%)	0.91	0.74-1.13
High School	4076 (21.8%)	265 (31.2%)	**5.01**	**3.24-8.00**
Less than High School	7041 (37.8%)	409 (48.3%)	**28.4**	**13.4-60.0**
Insurance type				
Private (ref)	5435 (25.6%)	47 (4.9%)	--	--
Medicaid/CHIP	14104 (66.3%)	792 (83.3%)	0.87	0.71-1.05
None/other	1718 (8.1%)	112 (11.8%)	**5.39**	**3.75-7.74**
Behavioral risk factors				
Alcohol				
No (ref)	16500 (75.7%)	845 (86.6%)	--	--
Yes	5285 (24.3%)	131 (13.4%)	**0.50**	**0.41-0.60**
Smoking				
No (ref)	19812 (90.9%)	886 (90.8%)	--	--
Yes	1976 (9.1%)	90 (9.2%)	1.02	0.82-1.26
Previous pregnancy information				
Number of previous pregnancies				
1	5628 (25.8%)	322 (33.0%)	**--**	**--**
2 or more	16167 (74.2%)	655 (67.0%)	**0.72**	**0.63-0.82**
Previous Preterm births				
No (ref)	19668 (90.2%)	899 (92.0%)	--	--
Yes	2127 (9.8%)	78 (7.9%)	0.81	0.64-1.02
Previous abortion				
No (ref)	15366 (70.5%)	730 (74.7%)	--	--
Yes	6429 (29.5%)	247 (25.3%)	0.82	0.71-0.94
Infections				
Lower Urinary tract infection				
Negative (ref)	20830 (95.6%)	895 (91.6%)	--	--
Positive	965 (4.4%)	82 (8.4%)	**1.90**	**1.53-2.36**
Bacterial Vaginosis				

Table 2.1. Maternal characteristics and prevalence rates by C. trachomatis status N=22,772, Continued

Variable	Chlamydia negative n (%)	Chlamydia positive n (%)	PR	95% CI
Negative (ref)	21327 (97.8%)	915 (93.7%)	--	--
Positive	468 (2.2%)	62 (6.3%)	**2.84**	**2.23-3.62**
Herpes Simplex Virus-2				
Negative (ref)	961 (62.1%)	586 (51.6%)	--	--
Positive	49 (37.9%)	46 (48.4%)	**1.50**	**1.02-2.22**
Hepatitis B				
Negative (ref)	21333 (99.3%)	953 (99.4%)	--	--
Positive	153 (0.7%)	6 (0.6%)	0.88	0.40-1.94
Neisseria gonorrhoeae				
Negative (ref)	21417 (99.7%)	873 (91.7%)	--	--
Positive	56 (0.3%)	79 (8.3%)	**14.9**	**12.8-17.5**
Group B Streptococcus				
Negative (ref)	15165 (76.7%)	673 (76.5%)	--	--
Positive	4596 (23.3%)	207 (23.5%)	1.01	0.87-1.18
Syphilis				
Negative (ref)	21423 (99.4%)	953 99.2%)	--	--
Positive	139 (0.6%)	8 (0.8%)	1.28	0.65-2.51
HIV				
Negative (ref)	17798 (99.2%)	790 (98.0%)	--	--
Positive	140 (0.8%)	16 (2.0%)	**2.41**	**1.51-3.86**
Current pregnancy				
Gestational age at first prenatal visit				
1-12 weeks (ref)	10700 (56.3%)	340 (39.7%)	--	--
13-27 weeks	6863 (36.1%)	422 (49.2%)	0.94	0.76-1.17
28-41 weeks	1448 (7.6%)	95 (11.1%)	**1.77**	**1.33-2.36**
Delivery outcome				
Live Birth (ref)	217490 (99.8%)	973 (99.6%)	--	--
Still birth	49 (0.2%)	4 (0.4%)	1.76	0.69-4.53
Intrauterine Growth Restriction				
No (ref)	21613 (99.2%)	970 (99.3%)	--	--
Yes	182 (0.8%)	7 (0.7%)	0.86	0.42-1.79
Delivery route				
Vaginal (ref)	15562 (71.5%)	740 (75.7%)	--	--
Cesarean	6209 (28.5%)	237 (24.3%)	**0.81**	**0.70-0.93**
Infant sex				
Female (ref)	10595 (48.7%)	465 (47.6%)	--	--
Male	11158 (51.3%)	511 (52.4%)	1.04	0.92-1.18

Modified Poisson regression with robust error measurements were used to calculate unadjusted prevalence rates

Table 2.2 displays associations between *C. trachomatis* and preterm birth subtypes. *C. trachomatis* was not significantly associated with overall preterm birth (model 3: RR=1.09 CI 95% 0.86-1.39) after full adjustments. However, there was a statistically significant association between *C. trachomatis* and medically indicated PTB after adjustments (model 3: RR=1.58 95% CI 1.09-2.28). Associations with C. trachomatis and term preeclampsia were also found in the fully adjusted model (model 3: RR=1.46 CI 95% 1.06-2.01). No other associations were found within the overall sample.

Table 2.2. Association between *Chlamydia trachomatis* and pregnancy outcomes among singleton pregnancies N=22,772, 2011-2017.

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
			RR (CI 95%)	RR (CI 95%)	RR (CI 95%)
			GA at delivery		
Term ≥ 37 weeks (ref)	20583 (90.6%)	874 (89.5%)	--	--	--
Preterm < 37 weeks	2040 (9.4%)	103 (10.5%)	1.13 (0.93-1.36)	1.10 (0.87-1.40)	1.09 (0.86-1.39)
Indicated PTB	683 (3.3%)	46 (4.1%)	**1.60 (1.11-2.30)**	**1.53 (1.13-2.07)**	**1.58 (1.09-2.28)**
Spontaneous PTB	730 (3.6%)	33 (3.6%)	1.02 (0.73-1.44)	0.88 (0.56-1.36)	0.86 (0.55-1.34)
			Preeclampsia (PE)		
Normotensive (ref)	18518 (93.0%)	806 (91.2%)	--	--	--
Overall PE	1389 (7.0%)	78 (8.8%)	**1.26 (1.02-1.57)**	1.24 (0.97-1.59)	1.19 (0.93-1.52)
Term PE	676 (3.4%)	50 (5.8%)	**1.66 (1.25-2.19)**	**1.50 (1.09-2.05)**	**1.46 (1.06-2.01)**
Preterm PE	713 (3.5%)	28 (3.4%)	0.90 (0.62-1.31)	0.97 (0.64-1.48)	0.90 (0.59-1.38)
			Chorioamnionitis		
No (ref)	20411 (94.5%)	895 (92.5%)	--	--	--
Yes	1196 (5.5%)	72 (7.5%)	**1.34 (1.07-1.69)**	1.05 (0.83-1.33)	0.95 (0.72-1.25)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*****Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, race, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

We did not have timing of infection available for analysis. However, most women are tested for *C. trachomatis* at the first prenatal visit. Accounting for gestational age at first prenatal visit did not alter the results. No significant associations were observed between *C. trachomatis* and preterm birth subtypes among women who initiated care in the first trimester. There was, however, an association with term preeclampsia in the fully adjusted model (model 3: RR=1.59 CI 95% 1.01-

2.51). Among women with second trimester initiation of care, *C. trachomatis* was associated with medically indicated preterm birth after full adjustments (model 2: RR=1.74 95% CI 1.03-2.95). No other associations were found in this group. Among women who initiate care in the third trimester, no significant associations were observed for any outcomes before or after adjustments [overall preterm birth (model 3: RR= 1.53 95% 0.68-3.44)].

As a secondary analysis, we explored associations between other genital infections and preterm birth subtypes. Bacterial vaginosis (2.33% 95% CI 0.214-0.253), HIV (0.83%, 95% CI 0.007-0.010), syphilis (0.65%, 95% CI 0.006-0.008), *Neisseria gonorrhoeae* (0.60% 95% CI 0.005-0.007), and hepatitis B (0.71% 95% CI 0.006-0.008) were of interest for this analysis. HIV was significantly associated with medically indicated preterm birth (model 3: RR=2.32 95% CI 1.31-4.11), spontaneous preterm birth (model 3: RR=2.36 95% CI 1.33-4.19), and preeclampsia with a term delivery (model 3: 1.98 95% CI 1.13-3.48). Syphilis was marginally associated with preeclampsia with a term delivery (model 3: RR=1.81 CI 95% 1.0-3.43). There were no associations found with *Neisseria gonorrhoeae* in any model.

2.3.2. Preterm birth subtypes by Race, Ethnicity and Foreign -born status

Chlamydia associated outcomes were examined by race, ethnicity, and foreign-born status. Among white women (n=3,959), a chlamydia associated medically indicated preterm was found all models (model 3: RR=2.30 CI 95% 1.06-5.01). No other associations were found among preterm birth subtypes. The sample of women with preeclampsia and positive chlamydia (n=1) was small and estimates could not be

calculated. Among Black women (n=2,971) there were no associations found with preterm birth or subtypes in any of the adjusted models. However, the risk of preeclampsia (model 3: RR=1.76 CI 95% 1.12-2.75) and term preeclampsia (model 3: RR=2.46 CI 95% 1.21-4.98) was significantly increased. Hispanic women (n=14,213) had no chlamydia associated pregnancy outcomes in fully adjusted models, but did have a marginally significant relationship with chlamydia and term preeclampsia (model 3: 1.39 CI 95% 0.97-2.00). Among foreign-born women (n=13,118), no fully adjusted models were significant with any outcome.

2.3.3. Age adjusted analysis

We determined if there were differences in the association between *C. trachomatis* and preterm birth subtypes by maternal age. In women < 25 years (n=5,654) (**Table 2.3**), *C. trachomatis infection* was significantly associated with medically indicated preterm birth after full adjustments (model 3: RR=2.25 95% CI 1.35-3.77) and with chorioamnionitis (model 3: RR=1.45 CI 95% 107-1.96). No other significant associations were found. Among women ≥25 years (n=17,118) shown in **Table 2.4**, *C. trachomatis* was significantly associated with term preeclampsia in the unadjusted (model 1: RR=1.64 CI 95% 1.07-2.52) but not the adjusted models (model 2: RR=1.50 CI 95% 0.92-2.47; model 3: RR=1.49 CI 95% 0.91-2.45).

Table 2.3. Association between Chlamydia trachomatis and pregnancy outcomes in singleton pregnancies for women < 25 years N=5619, 2011-2017.

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥] RR (CI 95%)	Model 2 [β] RR (CI 95%)	Model 3[±] RR (CI 95%)
GA at delivery					
Term ≥ 37 weeks (ref)	4677 (91.2%)	470 (89.3%)	--	--	--
Preterm < 37 weeks	451 (8.8%)	56 (10.6%)	1.21 (0.93-1.57)	1.29 (0.94-1.77)	1.31 (0.96-1.80)
Indicated PTB	124 (2.6%)	26 (5.2%)	**2.04 (1.35-3.08)**	**2.24 (1.34-3.72)**	**2.25 (1.35-3.77)**
Spontaneous PTB	179 (3.7%)	21 (4.3%)	1.16 (0.75-1.81)	1.18 (0.70-2.00)	1.19 (0.70-2.03)
Preeclampsia (PE)					
Normotensive (ref)	4323 (92.2%)	421 (90.1%)	--	--	--
Overall PE	368 (7.8%)	46 (9.8%)	1.26 (0.94-1.68)	1.36 (0.99-1.87)	1.32 (0.96-1.82)
Term PE	215 (4.7%)	29 (6.4%)	1.36 (0.93-1.98)	1.49 (0.99-2.24)	1.46 (0.96-2.21)
Preterm PE	153 (3.4%)	17 (3.9%)	1.14 (0.69-1.86)	1.23 (0.71-2.12)	1.18 (0.68-2.04)
Chorioamnionitis					
No (ref)	4645 (91.6%)	465 (89.4%)	--	--	--
Yes	427 (8.4%)	55 (10.6%)	1.26 (0.96-1.64)	**1.45 (1.07-1.94)**	**1.45 (1.07-1.96)**

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for race, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

Table 2.4. Association between Chlamydia trachomatis and pregnancy outcomes among singleton pregnancies among women ≥ 25 years N=17,118, 2011-2017.

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥] RR (CI 95%)	Model 2 [β] RR (CI 95%)	Model 3[±] RR (CI 95%)
GA at delivery					
Term ≥ 37 weeks (ref)	15078 (90.5%)	404 (89.6%)	--	--	--
Preterm < 37 weeks	1589 (9.5%)	47 (10.4%)	1.09 (0.83-1.44)	0.77 (0.53-1.13)	0.78 (0.53-1.14)
Indicated PTB	559 (3.6%)	20 (4.7%)	1.32 (0.86-2.04)	1.01 (0.57-1.76)	1.01 (0.57-1.78)
Spontaneous PTB	551 (3.5%)	12 (2.9%)	0.82 (0.47-1.44)	0.44 (0.18-1.05)	0.43 (0.18-1.04)
Preeclampsia (PE)					
Normotensive (ref)	14195 (93.3%)	385 (92.3%)	--	--	--
Overall PE	1021 (6.7%)	32 (7.7%)	1.14 (0.82-1.60)	1.03 (0.70-1.53)	1.01 (0.68-1.50)
Term PE	461 (3.1%)	21 (5.2%)	**1.64 (1.07-2.52)**	1.50 (0.92-2.47)	1.49 (0.91-2.45)
Preterm PE	560 (3.8%)	11 (2.8%)	0.73 (0.41-1.32)	0.63 (0.32-1.26)	0.61 (0.31-1.22)
Chorioamnionitis					
No (ref)	15762 (95.4%)	430 (96.2%)	--	--	--
Yes	769 (4.6%)	17 (3.8%)	0.82 (0.51-1.31)	0.90 (0.52-1.54)	0.88 (0.50-1.54)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for race, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

2.4. Discussion

Screening for *C. trachomatis* during pregnancy is significant since approximately 80% of infections are asymptomatic and may go undetected [110]. However, screening uptake is suboptimal in the population. A study of over 1 million pregnant women found that screening rates vary from 72% in young women (<25 years of age) to only 59% in older women, which is reflective of most screening recommendations [110]. Currently, CDC and the U.S. Preventive Service Task Force (USPSTF) have somewhat conflicting screening recommendations for pregnant women [101 111]. CDC recommends that all pregnant women under the age of 25 and older pregnant women at increased risk for an STI are screened at their first prenatal visit. Recommendations extend to the third trimester only if the women are under 25 or at continued high risk. USPSTF suggest pregnant women at increased risk of developing an STI are screened, but routine screening of women not at increased risk is not recommended [101]. Increased risk includes women with a previous STI diagnosis, multiple sexual partners, or have a history as a sex worker [101].

Among the entire cohort, there was a significant increase in the risk of medically indicated preterm birth, particularly earlier onset (<35 weeks), following prenatal chlamydia. After stratifying by race and ethnicity, the results showed that Black women were at increased risk of preeclampsia following prenatal chlamydia, while white women had increased risk of indicated preterm birth, while Hispanic women had marginal associations with term preeclampsia. Foreign born had no association with any outcomes following infections. Our results suggest that women in the lowest age

categories (<25) and white were at significant risk of *C. trachomatis* infection and subsequent medically indicated preterm birth, while Black women were at significant risk of infection and preeclampsia. However, those in the higher age category (≥25) seemed to trend towards an increased risk for term preeclampsia. Thus, our data found age-specific and race/ethnicity specific differences in the risk of adverse pregnancy outcomes following prenatal chlamydia as requested by Tao et al [59].

Medical indication for a preterm birth may include preeclampsia, small for gestational age, intrauterine growth restriction, unexpected bleeding, placental abruption, maternal chronic conditions and fetal distress [54 112]. Genital tract infections may cause systemic and local inflammation of the maternal/fetal membranes [54]. Inflammation is associated with several adverse pregnancy outcomes related to medically indicated preterm birth, including preeclampsia and growth restriction [113]. To the author's knowledge, no other study has found an association between *C. trachomatis* and medically indicated preterm birth. Furthermore, studies on maternal age and indication of preterm delivery are rare.

We found a marginal association between prenatal *C. trachomatis* and term preeclampsia, among Black women and older women. Although not statistically significant in the fully adjusted model, the effect size remained similar. Preeclampsia is a systemic maternal syndrome affecting 3-8% of pregnancies and is a leading cause of maternal mortality [114]. Furthermore, Black women are disproportionately affected by preeclampsia and related mortality in the United States [115]. Preeclampsia is clinically diagnosed by the new onset of hypertension and proteinuria or evidence of systemic

organ dysfunction [114]. Preeclampsia is considered a heterogeneous syndrome consisting of subtypes (e.g. early vs. late onset) with different underlying pathologies [116]. Prenatal *C. trachomatis,* infection may trigger an inflammatory response, which perhaps in older women increases the risk of preeclampsia later in gestation. Two studies have found associations between *C. trachomatis* and preeclampsia [57 58]. These studies suggested increases in trophoblast dysfunction after changes in uterine vascularization following *C. trachomatis* my lead to the maternal syndrome.

This study has several strengths. We utilized a robust dataset from a data repository that allowed differentiation of preterm birth subtypes [103]. Although misclassification of some variables with medical record data is possible, PeriBank cross checks medical records and data is imputed to limit this possibility. A few limitations persist, including generalizability due to the population being primarily Hispanic. However, Hispanics have a higher prevalence of chlamydia than whites and fewer prenatal chlamydia studies have focused on this group. Thus, our study adds to the current literature on prenatal chlamydia in Hispanic populations. Although adjustments were made for known confounders, there is still potential for residual confounding. Future analysis on complete data with previous pregnancy history and outcomes may allow for proper adjustments in the model. Treatment failure, re-infection and test of cure data was unavailable. Although, standard treatment for *C. trachomatis* has an efficacy of 97% [117]. We also did not have data on timing of infection, but used the gestational age of prenatal care initiation as an indicator of timing. Generally, chlamydia is screened at the first prenatal visit. We did find that women with chlamydia were more

likely to have a late first prenatal visit.

2.5. Conclusion

The objective of this study was to determine perinatal outcomes associated with prenatal *C. trachomatis*. This study suggested an association between *C. trachomatis* and medically indicated preterm birth among young white women, but not other preterm birth subtypes. We also found a significant relationship between *C. trachomatis* and term preeclampsia among Black and older women. It is possible that chlamydia triggers preeclampsia, and therefore early screening and treatment may reduce the likelihood of the onset of preeclampsia. Prospective evaluations are needed to better understand if maternal age modifies adverse outcomes following prenatal *C. trachomatis* and a larger more racially diverse sample may allow for the exploration of specific risk within separate groups.

3. EXAMINING STATISTICAL METHODS TO EVALUATE SYNDEMICS

3.1. Introduction

Syndemics theory proposes that disease risk and progression are influenced by multiple co-occurring or interacting factors. For example, multiple diseases, social conditions, and environment intermingle to modify the susceptibility and progression of a disease in an individual [64 70]. For infectious diseases, syndemics can intensify pathogenic contagiousness, accelerate virulence, and exaggerate symptoms [69]. Syndemics may work through alteration of immunological and biochemical processes such as stress induced immune degradation [64], and create changes in mental health and coping strategies [69]. Experiences of discrimination may further cause diseases to cluster, intensifying how social systems such as racism and sexism reinforce specific challenges that perpetuate epidemics within certain populations [68 118].

Applying a syndemic framework to sexual health and STI prevention is vital to advancing the development of culturally appropriate and targeted interventions to reduce disease among disparate populations [72]. For example, in a cross-sectional study of 564 HIV positive women of color, women who exhibited syndemics were less likely to virally suppressed, an indicator of treatment adherence in HIV positive individuals [71]. In another cross-sectional analysis of 467 sexual-minority women age 18-24, a syndemic defined as a combination of heavy alcohol consumption, polysubstance use, depressive symptoms, sexual behavioral risk factors and history of sexually transmitted infections (STIs) was associated with sexual orientation discrimination [68]. However, few studies

have examined syndemics in relations to STIs and methods to define a syndemic are not standardized.

Traditional approaches to evaluating syndemics in STIs and HIV have applied syndemic scoring statistical methodologies to quantifying co-occurring social and behavioral conditions [67 89 90]. Studies assign a score to social conditions and summarize those scores to indicate the presence of a syndemic, and the scale of the syndemic is dependent on the number of psychosocial indicators evaluated in the study. Higher values given to a syndemic through the generated score typically elucidates a dose-response effect. These syndemic scores are then incorporated into a logistic regression model to calculate the odds of disease. For instance, a cross-sectional evaluation of 300 male sex workers found that a syndemic score of four or more psychosocial health problems was associated with sexual risk behaviors [119]. A cross-sectional study of 82,812 adolescents in grade 7-12 found as the syndemic score (five or more indicators OR= 9.45 CI 95% 7.6-11.8) increased so did the risk of adolescent substance use, a factor that is related to STI risk [120]. In both studies, as the syndemic score increased risk was higher. In a longitudinal analysis of 799 HIV-uninfected women, a syndemic of low education, low income, unemployment, publicly funded health insurance, housing instability, substance and alcohol use, intimate partner violence, and previous incarceration was associated with increased risk of HIV [121].

Although syndemic scoring methods may provide some understanding of the intensity of a syndemic in a particular population, it may not allow for results that may be translated into practical applications [122]. Scoring methods were originally introduced

to select variables for subsequent interaction tests [70 90]. However, most studies only examine the syndemic score, which does not determine the interacting effects of co-occurring risks or conditions [90]. Indeed, Tsai and others [122-124] have extensively published on the limitations of syndemic scores indicating that the landmark syndemics study by Singer and Clair [70] explicitly states that summary methods are not adequate to detect interactions [90]. Thus, other methods to test for co-occurrence of factors leading to a syndemic need to be utilized [90]; such as latent class analysis [83 125 126].

Latent class analysis (LCA) is a finite mixture latent modeling approach that assists in identifying subgroups based on observed qualities or characteristics [127-129]. This approach assumes that a population contains latent subgroups that can be comprised of intersecting characteristics and is useful in identifying these subgroups using a multitude of observed characteristics across dimensions [130 131]. Social and behavioral health researchers have long used LCA as a tool to demonstrate unobserved categories that may explain observed outcomes such as HIV [83 125 126] and substance abuse [132-134]. Latent class can be applied to increase the understanding of the specific needs of a population. For example, a latent class analysis of 4,158 individuals from a longitudinal study revealed five classes of adolescent sexual behavior, of which, high risk classes were related to young adult STI rates [135]. Cleland and colleagues in a cross-sectional analysis of 2,853 Black and Hispanic adults, found that health literacy and emotional support were associated with substance use [133]. LCA is an emerging method to understand how syndemic factors affect individuals in a heterogeneous group. The results from this study may be useful in understanding the specific needs of young adults

for STI prevention and allow for the development of targeted prevention strategies for effective programs.

Robust statistical approaches to evaluate syndemics may allow for better interpretability of results and translation to prevention. Therefore, the purpose of this study is to conduct a syndemic score and latent class analysis to examine the syndemics of STI risk among a representative sample of young adults age 18-25 in the United States.

3.2. Methods

3.2.1. Study population

This was a cross-sectional analysis of individuals aged 18-25 interviewed for the National Health and Nutrition Examination Survey (NHANES) from two waves, 2011-2012 and 2013-2014. The NHANES is a multistage probability survey that incorporates sample weights for oversampling minority groups, clustering and stratum to be representative of the general United States population [136]. Data were collected through collaborations with the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) through physical exams and household and individual interviews [136]. Physical examinations were completed at a designated medical examination center (MEC), where anthropometric measures and biological samples were collected. A total of 15,869 adults aged 18 and older were interviewed between 2011-2014, and of those, 1,900 were aged 18-25. Individuals over the age of 25 (n=13,969) were excluded, and subjects were further excluded if they did not have a determinant test result for *Chlamydia trachomatis* (CT), Herpes simplex-2 (HSV-2), or Human

Immunodeficiency Virus (HIV) (n=97). The remaining 1,803 subjects were included for analysis.

3.2.2. Demographics

The NHANES provides a representative sampling of gender, age, and race for analytic purposes. Ages 18-25 were included for this analysis to observe adolescent and young adult syndemic characteristics, along with gender and race of the individual. Race was collected for non-Hispanic White, Non-Hispanic Black, Mexican American and Hispanic, Asian, mixed race and individuals that selected other race. As the sample of Asian, mixed and other race individuals was low, other, mixed race and Asians were combined to create a combined "other" category. Additional demographics of interested were head of household and household information such as number of people living in the household (1-4 or 5+), the country of birth (US or other) for the head of household, poverty index ratio (< 1.3), head of household education (high school graduate or less) and marital status (unmarried).

3.2.3. Sexual Transmitted Infections

Urinary and serum samples were used for laboratory analysis and confirmatory testing for STIs. *Chlamydia trachomatis* (CT) and Herpes Simplex Virus-2 (HSV-2) were diagnosed by nucleic acid amplification test (NAAT) [137] and HIV was diagnosed through synthetic peptide enzyme immunoassay (EIA) [101]. A composite variable for STI was created if subjects were positive for any of the STIs (*Chlamydia trachomatis*, Herpes Simplex Virus II, or HIV). These variables were included due to their consistency across years in NHANES and the low amount of missingness for each.

3.2.4. Mental health

Mental health was assessed using the 9-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is a widely used and well-validated screener of depression severity and symptoms in youth [138]. There were 9 questions assessing depressive symptoms in the two weeks before the survey with four response categories (0-3) denoting the occurrence and frequency of depressive symptoms. These were summed for an overall score ranging from 0 to 27 [139]. A score of 10 or greater is considered the threshold for depression, and was used as the cut point in this study [139].

3.2.5. Illicit drug use

The drug use questionnaire (DUQ) administered through the NHANES was used to assess past year use of marijuana or hashish, cocaine, heroin, and methamphetamine. Questionnaires are self-administered using the audio computer-assisted self-interview (ACASI) system and were conducted in the MEC. Questions asked, "Have you ever, even once, used marijuana or hashish?" and "Have you ever used cocaine, crack cocaine, heroin, or methamphetamine?" to establish baseline use of illicit drugs. Due to non-response and missingness in the more detailed questions, the ever use questions were the only included for this analysis.

3.2.6. Alcohol use

The alcohol use questionnaire assessed frequency of alcohol consumption in the past year. Participants were classified as regular alcohol users if they were men who reported having 1-2 drinks per day and women who reported having only 1 drink per day [140].

3.2.7. Smoking status

To accurately assess nicotine levels from tobacco smoking serum cotinine levels were assessed. The NHANES chooses to collected serum measures of cotinine for quantitative assessment of exposure. Cotinine is the primary metabolite of nicotine and is a biomarker for active and passive smoking. To adequately distinguish smokers from nonsmokers a cotinine level cut point of 3 ng/ml has been recommended [141]. In this study, participants were considered smokers if they had a serum cotinine level of greater than 3 ng/ml and a nonsmoker if 3 ng/ml or less.

3.2.8. Sexual behavior

Self-reported data on sexual behavior was obtained through ACASI in the MEC. Questions assessed whether participants had ever had sex, the age they first engaged in sex, and type of sex (anal, oral or vaginal). Questions were also asked about both lifetime and past year partners, whether partners were same or opposite sex, and specific same sex partner questions for both men and women. Several additional detailed questions were included in the self-reported survey, but due to non-response and missingness on those questions a subset of selected questions were used. Questions of interest include age at first sex, ever performed oral sex, ever performed anal sex, number of sex partners 5 years or older than the subject, number of sex partners in the past year, number of times subjects engaged in sex without a condom, and whether men were circumcised.

3.2.9. Statistical Analysis

Exploratory and univariate analyses were conducted to determine the distribution and frequency of each variable. Due to the NHANES design, variables are weighted to account for oversampling, nonresponse in the survey, and the probability design following the guidelines provided in the survey documentation [136]. Principal component analysis [142] was performed on variables that were similar indicators of socioeconomic status and sexual risk behaviors to reduce potential multicollinearity issues. Analyses were stratified by sex due to the differences in sexual risk indicators for both males and females [39 61 143]. Indicators for each measure included a score of 10 or more on the PHQ-9 to suggest depression, reporting at least 1 alcoholic beverage per day, ever using any illicit drug, having a sexual debut younger than 15 years old, reporting ever having oral or anal sex, having any partners that were 5 years or older than the individual, and reporting ever having sex without a condom.

Composite variables were created from each of these individual indicator variables. A new indicator was created to signify the presence of the variable (e.g., if depression was present, depression=1, if no depression, depression=0) then the indicators were summed to create a composite variable "syndemic score". Scores were assigned to depression, regular alcohol use, any drug use including marijuana, smoking, and the presence of sexual behavioral risk factors. A composite range of 0-9 was established based on the number of reported syndemics for each group. The frequencies and percentages of the syndemics were calculated, and then PROC LOGISTIC in SAS V9.4 was used for multivariable logistic regression to determine the association between

the syndemic score and STI. Common sociodemographic indicators associated with STI risk are young age, race/ethnicity other than white, and indicators of low socioeconomic status [144]. Principle component analysis was conducted using each of the sociodemographic indicators to determine highly correlated variables. Among the highly correlated variables, one was chosen for regression. Therefore, regression models were adjusted for race, country of birth, poverty index ratio (PIR), number of people living in household, and the head of household country of origin, education level, and marital status. Odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (CI) are reported.

LCA for men and women were performed using PROC LCA version 1.3.2, SAS V9.4, Cary NC [145]. All analyses incorporated sample weights. Model selection was achieved by examining common measures of model fits including the G^2 likelihood ratio chi square test, the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and entropy to compare models [128]. In each of these criteria, with the exception of entropy, lower values suggest optimal parsimony and model fit. Entropy is a measure of the model's ability to separate clusters. An entropy approaching 1 is an indicator of better separated classes which delineate from each other and suggests a better fitting model [146]. Missing data were handled with the maximum likelihood expectation maximization procedure and assumed to be missing at random in PROC LCA. The association between class membership and STIs was obtained using logistic regression. Odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (CI) are reported. Adjustments included the same variables as the composite analysis regression.

3.3. Results

3.3.1. Descriptive results

The composition of the sample was relatively diverse in age (mean: 21.1, SD: 2.4) and race (32% Non-Hispanic White, 26% Non-Hispanic Black, 25% Hispanic, 12% Asian, and 5% other) as described in **Table 3.1**. Roughly, 30% reported a head of household that was foreign born, 36% reported a head of household with some college education, and 58% had unmarried heads of household. STI positivity was 9% (HIV-0.12%, HSV-5.6%, Chlamydia-4.6%), the prevalence of depression was 7%, regular alcohol use was 44%, and smoking was 29%. Ever using marijuana was 42% and ever using cocaine, heroin, or methamphetamine was 8%. Majority of the sample reported ever engaging in oral sex (68%) and inconsistent condom use (76%), while smaller proportions reported anal sex (27%), older partners (30%), and more than 1 partner in the past year (30%).

Table 3.1. Demographic characteristics for sample of young adults 2011-2014, N=1803.

Variable/Label		N (%)	Mean (SD)	Missing (n)
Gender	Male	908 (50.36)		
	Female	895 (49.64)		
Age	18-25		21.1 (2.36)	
Race	White	573 (31.78)		
	Black	478 (26.51)		
	Hispanic	447 (24.79)		
	Asian	213 (11.81)		
	Other	92 (5.10)		
Citizen	Yes	1566 (86.95)		2
	No	235 (13.05)		
Country of origin	US	1464 (81.20)		
	Non-US	339 (18.80)		
Poverty Index Ratio	$\leq$ 1.3	860 (51.71)		140
	> 1.3	803 (48.29)		
Number of people living in household	1-2	403 (22.35)		
	3-4	798 (44.26)		
	5-6	434 (24.07)		
	7 or more	168 (9.32)		
Head of household country of origin	US	1196 (70.60)		109
	Non-US	498 (29.40)		
Head of household education level	College grad	299 (17.69)		113
	Some college	613 (36.27)		
	HS grad	409 (24.20)		
	Less than HS	369 (21.83)		
Head of household marital status	Married	702 (42.24)		141
	Not Married	960 (57.76)		
Chlamydia	Negative	1705 (95.36)		15
	Positive	83 (4.64)		
HIV	Negative	1669 (99.88)		132
	Positive	2 (0.12)		
HSVII	Negative	1578 (94.43)		132
	Positive	93 (5.57)		
STI (Test for Chlamydia, HIV, HSVII)	Negative	1633 (90.57)		
	Positive	170 (9.43)		
Depressed	No	1540 (92.88)		145
	Yes	118 (7.12)		
Had at least 12 alcohol drinks/1 yr.?	No	560 (33.63)		138
	Yes	1105 (66.37)		
1-2 alcoholic drinks/day - past 12 mos.?	No	660 (55.65)		617
	Yes	526 (44.35)		
Ever have 5 or more drinks every day?	No	1167 (92.03)		535
	Yes	101 (7.97)		
Serum cotinine level $\leq$ 3 or > 3	Nonsmoker ($\leq$ 3)	1276 (70.77)		
	Smoker (> 3)	527 (29.23)		
How old when you first had sex	$\leq$ 15	893 (49.53)		
	>16	910 (50.47)		
Ever performed oral sex on a woman or a man (male and female combined)	Yes	1120 (67.71)		149
	No	534 (32.29)		

Table 3.1. Demographic characteristics for sample of young adults 2011-2014, N=1803, Continued

Variable/Label		N (%)	Mean (SD)	Missing (n)
Number of sex partners 5 years or older than you	0 1≥	921 (70.20) 391 (29.80)		491
# of sex partners in the past year (male and female combined)	0-1 2≥	1156 (70.06) 494 (29.94)		153
Number of times you had sex without a condom	Never/always condom Ever/no condom used	300 (23.96) 952 (76.04)		551
Circumcised or uncircumcised (males only)	Circumcised Uncircumcised	538 (69.42) 237 (30.58)		1028
Ever used marijuana	Yes No	960 (58.01) 695 (41.99)		148
Ever used cocaine/heroin/methamphetamine	Yes No	128 (7.73) 1526 (92.21)		149

3.3.2. Composite scores

The mean number of reported indicators was 2.3 (SD: 2.4) among the sample. The odds of a positive STI result increased with the number of indicators. The gender-specific analysis is shown in **Table 3.2**, and suggests males reporting 3-5 indicators (35.9%) (AOR: 2.10 CI 95% 1.0-4.2) and six or more indicators (13%) (AOR: 2.84 CI 95% 1.2-6.7) had a significantly increased odds of STI after adjustments. Females had a significantly increased odds of STI when they reported six or more indicators (11.0%) (AOR: 3.20 CI 95% 1.7-6.0) after adjustments.

Table 3.2. Association of interrelated social and behavioral categories (syndemic) and STI positivity among males and females 18-25, NHANES 2011-2014.

Number of social and behavioral indicators present (N, %)	STI positive			
	Unadjusted odds ratio (95% CI)	p-values	Adjusted odds ratio* (95% CI)	p-values
Males				
0-2 (464, 51.10%) reference	--	--	--	--
3-5 (326, 35.90%)	**2.33 (1.26-4.28)**	**0.0066**	**2.10 (1.04-4.25)**	**0.0378**
6+ (118, 13.00%)	**2.55 (1.17-5.55)**	**0.0187**	**2.84 (1.21-6.70)**	**0.0168**
Females				
0-2 (490, 54.75%) reference	--	--	--	--
3-5 (307, 34.30%)	**1.57 (1.01-2.45)**	**0.0452**	1.39 (0.84-2.29)	0.2040
6+ (98, 10.95%)	**3.13 (1.80-5.43)**	**<0.0001**	**3.20 (1.71-6.02)**	**0.0003**

Social/behavioral indicators include depression, regular alcohol use, smoking, ever using drugs, age at first sex, any anal or oral sex in the past year, any partners 5 years or older in the past year, greater than 1 partner in the past year, and ever sex without a condom in the past year.
Bolded values indicate $p < 0.05$.
*Adjustments are for demographic characteristics listed in Table 1. (race, country of birth, PIR, number of people living in household, and head of household country of origin, education level, and marital status).

No other significant relationships were observed from the composite score analysis.

3.3.3. Latent Class Analysis

A four class model was selected for males and a three class model for females. Models were selected if they showed the greatest distinction between classes and provided the best interpretability (**Table 3.3**).

Table 3.3. Fit statistics for LCA model selection in men and women age 18-25, NHANES 2011-2014.

Sex	No. of Classes	Log likelihood	Likelihood Ratio G^2	Degrees of freedom	AIC	BIC	Entropy
Men N=908	1	-4649.05	1352.46	1013	1372.46	1420.57	1.00
	2	-4382.38	819.12	1002	861.12	962.16	0.64
	3	-4294.08	642.53	991	706.53	860.49	0.68
	4*	**-4257.10**	**568.55**	**980**	**654.55**	**861.44**	**0.71**
	5	-4223.87	502.10	969	610.10	869.90	0.67
	6	-4205.61	465.58	958	595.58	908.31	0.70
Women N=895	1	-4553.41	1325.23	1013	1345.23	1393.19	1.00
	2	-4303.49	825.38	1002	867.38	968.11	0.62
	3*	**-4217.20**	**652.80**	**991**	**716.80**	**870.30**	**0.65**
	4	-4204.44	627.27	980	713.27	919.53	0.63
	5	-4176.46	571.33	969	679.33	938.35	0.69
	6	-4167.17	552.73	958	682.73	994.52	0.80

*Indicates selected model
Model selection was achieved by examining the G^2 likelihood ratio chi square test, the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and entropy. With the exception of entropy, lower values suggest optimal parsimony and model fit. The BIC and entropy were used for model selection in both sexes as the AIC favored more complex models. After reviewing the models and class memberships, the four class model was chosen in males and females.

Table 3.4 shows class membership probabilities for men. Class one (28%) was the second largest class and reported the least indicators of any group; class one was used as the reference class in the regression models. Class two (15%) indicated the highest proportion of men who had partners that were 5 years or older (38%), but reported a lower probability of other indicators. Participants in class three (37%), the largest class in men, reported the highest proportion of smoking (61%), oral (98%) and anal sex (58%), reported two or more partners in the past year (64%), and had the highest probability of reporting inconsistent condom use (86%). Males in class 4 (19%)

had the highest probability of reporting depression (8%), regular alcohol use (71%), early sexual debut (86%), and ever using any drugs (96%). When compared to class one, males in class three had significantly increased odds of STI (AOR: 2.42 CI 95% 1.1-5.4) after adjustments. No other associations were found among men and no co-occurring social factors seemed to increase the risk of STIs (e.g. syndemic).

Table 3.4. Class membership (%) and probability of response in male (n=908) participants age 18-25, NHANES 2011-2014.

Item/Variable	Class 1 (n=252, 27.75%)	Class 2 (n=141, 15.53%)	Class 3 (n=339, 37.33%)	Class 4 (n=176, 19.38%)
Depressed	0.0135	0.0595	0.0600	**0.0766**
Regular alcohol use	0.3675	0.3500	0.1699	**0.7103**
Smoker	0.1232	0.3778	**0.6097**	0.0000
Age at first sex < 15	0.1798	0.5222	0.6352	**0.8642**
Oral sex	0.9176	0.0000	**0.9776**	0.0000
Anal sex	0.1992	0.0296	**0.5822**	0.0071
Partners 5yr +	0.0777	**0.3809**	0.3701	0.0510
2 + partners	0.2319	0.0961	**0.6429**	0.0000
Inconsistent condom	0.7277	0.5590	**0.8567**	0.5983
Ever used any drug	0.4519	0.1806	0.0804	**0.9572**
Odds of STI	(reference)	Class 2 vs class 1 OR=1.65 (CI 95% 0.6-4.2) *OR_{adj}=1.62 (CI 95% 0.6-4.4)	Class 3 vs class 1 *¥**OR=2.96** **(CI 95% 1.4-6.1)** *¥**OR_{adj}=2.42** **(CI 95% 1.1-5.4)**	Class 4 vs class 2 OR=0.14 (CI 95% 0.02-1.1) *OR_{adj}=0.17 (CI 95% 0.02-1.4)

*Adjustments are for demographic characteristics listed in Table 1. (race, country of birth, PIR, number of people living in household, and head of household country of origin, education level, and marital status).
¥Indicates values are significant.

Membership probabilities and class composition for women are shown in **Table 3.5**. Class one (37%) was the largest class and was comprised of women reporting a low probability of each of the indicators, which was used as the reference class for regression. Among women in class two (33%), regular alcohol use (73%) and early sexual debut (68%) were the highest reported probabilities. Class three (29%) reported the highest conditional probability of depression (23%), smoking (61%), oral sex (99%), anal sex (55%), older partners (42%), two or more partners in the past year (49%), inconsistent condom use (86%) and any drug use (86%). Women in this class seemed to exhibit a syndemic of depression, smoking, drug use and sexual risk behaviors. In reference to class one, women in class three had a significantly increased odds of STI (AOR: 2.19 CI 95% 1.2-3.8) after adjustments. No other significant associations were found among women. Class three indicates a possible syndemic of depression and negative coping strategies to increase STI within young women in the US.

Table 3.5. Class membership (%) and probability of response in female (n=895) participants age 18-25, NHANES 2011-2014.

Item/Variable	Class 1 (n=345, 38.58%)	Class 2 (n=228, 25.51%)	Class 3 (n=322, 35.91%)
Depressed	0.0415	0.0425	**0.2332**
Regular alcohol use	0.6513	**0.7268**	0.3969
Smoker	0.0156	0.1135	**0.6085**
Age at first sex < 15	**0.8015**	0.3198	0.4462
Oral sex	0.9768	0.1527	**0.9859**
Anal sex	0.3440	0.0000	**0.5536**
Partners 5yr +	0.1717	0.3532	**0.4254**
2 + partners	0.2066	0.0228	**0.4858**
Inconsistent condom	0.7991	0.6465	**0.8654**
Ever used any drug (including marijuana)	0.5553	**0.7725**	0.0818
Odds of STI	(Reference)	Class 2 vs class 1 OR= 1.27 (CI 95% 0.75-2.15) *OR_{adj}=1.49 (CI 95% 0.80-2.77)	Class 3 vs class 1 **OR= 2.65** **(CI 95% 1.63-4.31)** ***OR_{adj}= 2.31** **(CI 95% 1.32-4.05)**

*Adjustments are for demographic characteristics listed in Table 1. race, country of birth, pir, number of people living in household, and head of household country of origin, education level, and marital status).

3.4. Discussion

Understanding syndemic factors for sexually transmitted infections is particularly important in late adolescents and early adulthood. In 2008, A US evaluation of the prevalence of STIs determined that women age 15-24 represented an estimated 660,000 cases of chlamydia [8] and that rates varied by race/ethnicity indicating the persistence of disparities [147]. Few studies have used nationally representative data to examine appropriate statistical measures to identify syndemics for recommending widespread prevention activities.

In our study we sought to examine common statistical approaches to identify syndemics within the population. Using the syndemic scoring method, the most common

approach, we found that as the syndemic score increased so did the odds of STI in men, but was only increased for women reporting six or more indicators. This method suggests that as the number of risk factors increase the odds of STI also increase. A syndemic scoring approach may reveal risk related to multiple, simultaneously occurring conditions in a specific group. However, syndemic scoring methods are typically unable to determine the specific psychosocial factors related to increased risk of infection among certain groups.

In this study, the syndemic scoring method did not reveal any differences in the social and behavioral indicators for men and women therefore did not reveal any useful information related to the conditions of the individuals at increased risk of STI. Similar to this study, a cross-sectional survey of 300 male sex workers in Vietnam used a syndemic scoring method to identify a syndemic related to unprotected anal sex, a sexual behavioral indicator that increases the risk of HIV [119]. The findings suggested that a higher syndemic score included psychosocial conditions that increased the risk of HIV acquired through unprotected anal sex among male sex workers. However, the specific needs of those sex workers were undetermined because the syndemic score was unable to reveal the prevalence of the psychosocial conditions that were co-occurring.

Similarly, a cross sectional analysis of 2,020 men who have sex with men in Latin American determined that the presence of more psychosocial factors were related to being less likely to adhere to antiretroviral therapy [93]. Again, a syndemic score that included social and behavioral indicators increased the risk of negative treatment

adherence, but did not result in specific indicators and how those indicators co-occur to increase the risk of negative drug adherence.

A latent class analysis was used in the present study to examined psychosocial indicators to determine which variables were co-occurring to increase the risk of STI. In men, the LCA revealed a class that consisted of co-occurrence of depression and substance use, but individuals in this group did not have increased risk of STI. Males with a higher probability of smoking and sexual risk behaviors were at increased risk of STI. A syndemic was not evident among men because the prevalent indicators were sexual behaviors which are known to directly increase STI risk. Among women, a syndemic of depression, drug use and smoking co-occurred with sexual risk behaviors to increase the risk of STI. This syndemic was particularly informative because it allowed the observation of specific characteristics of the women who were at increased odds for STI.

Our study had similar findings to a longitudinal study of 4,158 high school sophomores, juniors, and seniors examining their risk for STI [135]. Authors determined classes at increased risk of STI also exhibited depressive symptoms and substance use. These results are useful in identify a target population, giving a specific understanding of the problems co-occurring with sexual risk behaviors, and can inform prevention efforts on how to formulate interventions to optimize effectiveness. For example, women from our study may need an intervention that addresses their mental health and coping strategies to optimize their ability to negotiate sexual practices that reduce their risk of STI.

Latent class analysis is particularly useful because of its limited number of assumptions, its' person-centered approach, and its ability to allow multiple intersecting measured characteristics in the model when the population evaluated is hypothesized to have an underlying latent construct, such as syndemics [127]. The greatest benefit of LCA is its ability to separate subjects into heterogeneous groups that identify similar reported indicators and risk of STIs.

Additionally, structural equation models (SEM) have been suggested to examine syndemic pathways to increase STI risk. SEM are path analyses that allow for multiple indicators of latent constructs to estimate the linear relationship between the latent variables and indicator or observed variables [148]. SEM was adopted as a robust analysis due to its ability to consider simultaneous models, endogenous and exogenous variables, and handle continuous, ordinal, dichotomous or censored variables[149]. In syndemics research, SEM has been used to determine the direct and indirect effects of indicators on syndemic latent variables in a number of subject areas. These include, discrimination [68], substance use [20 132], violence and depression [85 150 151], suicidality [152] and HIV and STI risk [153]. SEM is an additional useful tool in understanding how variables are structured together and may be a useful alternative for providing information on the multiple linear relationships that may be present simultaneously on a syndemic pathway.

While each of the models are useful, there are limitations. Syndemic scoring approaches tell little about the relationship between indicators and how they may interact to influence increasing risk. Furthermore, required assumptions are that the variables included are of the same importance [122]. The latent class approach has no normality

assumptions, but ignore some uncertainty that may arise in class predictions [122]. Furthermore, latent class requires categorical formats for data, requiring the recoding of continuous variables that may lose their importance in a different format [127]. In this study, we included original categorical variables and included widely used and validated cut-points for continuous variables that were converted into categories. Some limitations to this study include the lack of the most recent NHANES data, which was not fully updated at the time of this analysis, the exclusion of "other" race groups (such as Asians) due to their small sample, and cross-sectional nature of this study design that limits inferences about timing of the syndemics found.

3.5. Conclusion

Identifying the most appropriate models for syndemic research is imperative when conducting analysis using population level data. Techniques need to be both statistically and qualitatively informative and provide robust estimates for both smaller and large samples. In this analysis, the latent class model provided the most robust estimates concerning risk for sexually transmitted infection and identified co-occurring indicators that may increase the risk of STI among a nationally representative sample of young adults aged 18-25. The findings suggest that scoring approaches give little to determine the presence of a syndemic, and do not produce information that can be useful in formulating interventions. Most importantly, the composite score shows that men need fewer and more behavioral risk factors to increase their risk of STI while women reporting a greater number of risk factors had an increased risk of STI. Latent class analysis was able to determine the exact indicators that co-occurred, the prevalence of

reporting those indicators among the group of individuals with them, and can be useful to detail problems that must be addressed in intervention development. Using techniques that are informative on heterogeneous groups can provide direct translation into practice for prevention strategies and can allow for social, environmental, and behavioral risk factors that influence STI risk to be addressed simultaneously.

4. EXAMINING RACIAL/ETHNIC PROFILES OF SEXUALLY TRASNMITTED INFECTION RISK IN YOUNG ADULTS USING A LATENT CLASS ANALYSIS*

4.1. Introduction

Adolescence and young adulthood are important periods for the development of intimate relationships and are characterized by risk behaviors such as unprotected sex, increasing rates of substance use, and the exacerbation of health and social disparities [15]. These developmental periods are also associated with increased incidence of depression. For example, as many as one in five American adolescents suffers from a diagnosable depressive episode by age 18 [154]. Substance use, social relationships, mental health, risky behavior and sexually transmitted infections (STIs) are highly interrelated [155]. STIs have a significant public health impact as their effects range from reproductive sequelae (e.g. infertility) to chronic health conditions [156]. Adolescents and young adults account for half of all new STIs in the United States making them an important group for risk reduction [156]. However, interventions that target known individual risk factors have not been successful in reducing STI rates or racial/ethnic and sex specific disparities in STIs [45].

The development and progression of sexual behaviors and risk of STIs varies as a function of race/ethnicity and sex. For example, striking disparities exist in *Chlamydia trachomatis* prevalence with Hispanic and Black women having much higher rates than non-Hispanic whites [11], even after adjusting for individual and population level risk

factors [157]. Significant disparities exist between sexes in the development of substance use, STI/HIV risk behaviors, STI/HIV transmission and reproductive health outcomes. Sex and racial/ethnic differences in risk behavior also persist. For instance, females tend to have fewer sex partners and report less binge-drinking but have a higher risk of STIs than males [143]. Risk behaviors may also interact differently as a function of race/ethnicity and sex. For example, rates of receptive anal sex are positively related to binge drinking in females but not males [158]. Black females are less likely to report high risk behaviors (e.g. lifetime partners, unprotected sex, substance use) but are consistently more likely to test positive for STIs [61].

Traditional disease control programs with singularly focused interventions neglect broader perspectives [63] and are insensitive to marginalized experiences that contribute to poor sexual health [78]. Syndemic theory suggests that the convergence of social, environmental and ecological factors often produce difficult environments that promote disease [159]. Understanding the syndemics of STIs in adolescents and young adults may provide a unique opportunity to develop effective and culturally appropriate interventions that target high risk, hard to reach groups. The syndemics literature has overwhelmingly focused on HIV in men who have sex with men (MSM) or sexual minorities, and have not considered effect modification by sex or race/ethnicity [66 160]. Furthermore, these studies have misclassified syndemics with the use of syndemic scoring methods. The objective of this study is to use latent class analysis (LCA), a type of finite mixture modeling approach that identifies subgroups based on observed qualities or characteristics [128], to identify patterns of STI risk using variables available in

a large, nationally representative dataset. It is hypothesized that the co-occurrence of multiple risk categories will increase the probability of STIs and are unique to groups defined by sex and race/ethnicity.

4.2. Methods

4.2.1. Study population

This was a cross-sectional analysis of individuals aged 18-25 interviewed in the National Health and Nutrition Examination Survey (NHANES) in waves 2011-2012 and 2013-2014. NHANES is a multistage probability survey with complex design to be representative of the general United States population [136]. Data collection methods are explained elsewhere [136]. We excluded subjects without a determinant STI test result (see below for description of STIs) (n=236), resulting in a sample of 1,664 participants with complete data.

4.2.2. Demographics

This study focused on white, non-Hispanic black, and Hispanic individuals because the samples were large enough to use LCA with subgroup analysis of risk for a positive STI test. Other demographics of interest were number of people living in the household (1-4 or 5+), country of birth of the head of household (US or other), poverty index ratio ($\leq$ 1.3), head of household education (high school graduate or less), and head of household marital status (unmarried).

4.2.3. Sexually Transmitted Infections

Urinary and serum blood samples were used for laboratory analysis and confirmatory testing for STIs. *Chlamydia trachomatis* (CT) and Herpes Simplex Virus-2

(HSV-2) were diagnosed by nucleic acid amplification test (NAAT) and HIV was diagnosed through synthetic peptide enzyme immunoassay (EIA) [101]. A composite variable for STI was created if subjects were positive for any of the STIs (*Chlamydia trachomatis*, Herpes Simplex Virus II, or HIV).

4.2.4. Mental health

Mental health was assessed using the 9-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is a widely used and well-validated screener of depression severity and symptoms in youth [138]. There were 9 questions assessing depressive symptoms in the two weeks before the survey with four response categories (0-3) denoting the occurrence and frequency of depressive symptoms. These were summed for an overall score ranging from 0 to 27 [139]. A score of 10 or greater is considered the threshold for depression, and was used as the cut point in this study [139].

4.2.5. Illicit drug use

The drug use questionnaire (DUQ) administered through the NHANES was used to assess past year use of marijuana or hashish, cocaine, heroin, and methamphetamine. Due to non-response and missingness in the more detailed questions, these ever use questions were used in this analysis.

4.2.6. Alcohol use

The alcohol use questionnaire assessed frequency of alcohol consumption in the past year. Participants were classified into one of three alcohol use groups: (1) abstainers, those who had less than 12 drinks in their lifetime; (2) moderate alcohol users, men who have 1-2 drinks per day and women who have no more than 1 drink per

day; and (3) excessive alcohol users, men who have 5 or more drinks in one day or women who have 4 or more drinks in one day [140].

4.2.7. Smoking status

Cotinine is the primary metabolite of nicotine and is a biomarker for active and passive smoking. To adequately distinguish smokers from nonsmokers a cotinine level cut point of 3 ng/ml was recommended [141]. In this study, participants were considered smokers if they had a serum cotinine level of greater than 3 ng/ml and a nonsmoker if 3 ng/ml or less.

4.2.8. Sexual behavior

Participants were asked if they had ever had sex, the age they first engaged in sex, and what type of sex (anal, oral or vaginal) via audio-computer-assisted self-interview (ACASI). Additional questions included number of partners, times subjects engaged in sex without a condom, and whether the male subjects were circumcised.

4.2.9. Statistical Analysis

LCA was used to identify syndemics profiles of demographic characteristics, mental health, substance use, and sexual risk behaviors among 18 to 25 year old's in the NHANES. A total of 18 variables were included in the LCA to determine syndemic patterns by race/ethnicity among each gender. Measurement invariance was imposed to test whether the latent classes were similar or different across gender. In this sample, measurement invariance did not hold because the difference between the freely estimated model and the constrained model displayed significant differences in responses between sexes ($p<0.0001$). Therefore, separate models were examined for

each sex. All analyses were performed in SAS software (Version 9.4, Cary, NC). The LCA was completed using the LCA Procedure, version 1.3.2 [145]. All analyses incorporated sample weights to account for NHANES survey design. Model selection was achieved by examining common measures of model fit including the G^2 likelihood ratio chi square test, the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and entropy [127]. On each of these criteria, with the exception of entropy, lower values suggest optimal parsimony and model fit. Multiple groups LCA were run by race (*white, non-Hispanic black, and Hispanic)* to test differences between groups. Race was added as a grouping variable and fit statistics were compared to determine appropriate model fit. The association between class membership and STIs was estimated for each sex using logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

4.3. Results

4.3.1. Descriptive results

STI positivity was 11% in the sample (HIV= 1.2%, CT=5.0%, HSV-2=5.6%). Roughly 7% reported depression, 8% excessive alcohol use, and 31% were smokers. The majority of participants reported engaging in oral sex (68%), while only 28% indicated anal sex. Two-thirds had not used a condom during sex at least once in the past year, 30% had a partner who was five years or older, and 30% had greater than two sex partners in the past year. The majority of participants reported marijuana use (58%), whereas only 8% had reported heroin, cocaine, or methamphetamine use.

4.3.2. Latent classes by race

To address known racial disparities in STI risk, multiple-group LCA was conducted by race in each sex group separately. Three class solutions were selected as they provided enough distinctions between the classes, retained an adequate sample size within each class, and allowed for interpretability for class membership (**Table 4.1**).

Table 4.1. Fit statistics for LCA model selection in females and males.

Sex	No. of Classes	Log likelihood	Likelihood Ratio G^2	Degrees of freedom	AIC	BIC	Entropy
Female N=830	1	-7028.84	4418.42	131054	4452.42	4532.68	1.00
	2	-6703.97	3768.66	131036	3838.66	4003.91	0.68
	3*	-6617.86	3596.45	121018	3702.45	3952.69	0.68
	4	-6585.26	3531.24	131000	3673.24	4008.46	0.71
	5	-6548.31	3457.35	130982	3635.35	4055.56	0.68
	6	-6510.35	3381.44	130964	3595.44	4100.63	0.74
	7	-64.96.60	33.54.53	130946	3604.53	4194.71	0.71
Male N=834							
	1	-7609.60	5397.32	262125	5433.32	5518.40	1.00
	2	-7245.38	4668.89	262106	4742.89	4917.76	0.70
	3*	-7138.44	4455.00	262087	4567.00	4831.67	0.70
	4	-7054.28	4286.68	262068	4436.68	4791.15	0.70
	5	-7003.11	4184.35	262049	4372.35	4816.61	0.72
	6	-6964.40	4106.93	262030	4332.93	4866.99	0.74
	7	-6907.00	3992.14	262011	4256.14	4880.00	0.76

*Indicates selected model

Model selection was achieved by examining the G2 likelihood ratio chi square test, the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and entropy. With the exception of entropy, lower values suggest optimal parsimony and model fit. The BIC and entropy were used for model selection in both sexes as the AIC favored more complex models. After reviewing the models and class memberships, the four class model was chosen in males and females.

Profiles in women by race varied (**Table 4.2**). White women in class 1 (high risk) included a high chance of unmarried head of household, illicit drug use, anal sex,

smoking and depression. Class 2 white women reported the lowest chance of risky sexual behavior, and primarily reported regular alcohol use with very little drug use. Class 3 reported some risky sexual behaviors, and drug use. Young white women in class 1 had a nearly tenfold increase in their odds of STI (OR=2.9 95% CI 1.3-27.2) when compared to the low risk class (class 2, reference). No other associations were found.

Class 1 in black young women was considered the high risk profile and contained low income indicators, a high chance of reporting depression, excessive alcohol use and smoking (**Table 4.2**). In class 2, women reported similar demographics as class 1, but lower risky sexual behaviors and regular alcohol use. Class 3 contained black women with unmarried head of households, sexual risk behaviors and some marijuana use. Interestingly, none of the classes in black women reported any illicit drug use. Compared to low-risk white young women (class 2), black young women in class 1 had a significantly increased odds of STI (OR=9.9 95% CI 2.1-46.3). No other associations were found.

Among Hispanic young women there was a high chance of being low income across all classes. Class 1 included the highest chance of risky sexual behaviors with some low income characteristics. Class 2 included Hispanic women with low income (**Table 4.2**). Class 3 contained low income, high chance of risky sexual behavior, and illicit drug use. When compared to white women in class 2 (referent group), Hispanic women in class 3 had a nine fold increase in their odds of STI (OR=9.5 95% CI 1.8-51.3).

Table 4.2. Latent class membership and probabilities (%) for syndemic indicators in females by race, NHANES 2011-2014. (adapted from 161)

Race	White, n=250			Black, n=234			Hispanic, n=223		
Item/Variable	Class 1 (28.88%, n=72)	Class 2 (26.04%, n=65)	Class 3 (45.08%, n=113)	Class 1 (22.76%, n=53)	Class 2 (57.82%, n=135)	Class 3 (19.42%, n=46)	Class 1 (13.14%, n=29)	Class 2 (60.43%, n=135)	Class 3 (26.43%, n=59)
5+ in house	**0.2383**	0.1933	0.1950	0.2536	**0.3669**	0.0756	0.0282	0.4591	**0.4662**
HS grad or less	**0.3622**	0.2771	0.3491	**0.6416**	0.4928	0.0934	**0.7068**	0.6806	0.4985
PIR low-income	**0.4894**	0.3045	0.3698	**0.8087**	0.5432	0.5156	**0.6959**	0.5672	0.6240
HH Country non-US	0.0000	**0.1062**	0.0850	0.0258	**0.1074**	0.0671	0.3330	**0.6574**	0.5535
HH unmarried	**0.7643**	0.4508	0.5003	0.8326	0.6284	**0.9808**	**0.9040**	0.4409	0.5657
Depressed	**0.2971**	0.0927	0.0757	**0.2577**	0.0404	0.0231	**0.4116**	0.0099	0.0612
Regular alcohol use	0.4566	**0.8064**	0.4209	0.4366	**0.7513**	0.4735	0.0000	**0.6202**	0.4956
Excessive alcohol use	**0.1615**	0.0000	0.0000	**0.2420**	0.0105	0.0549	**0.1850**	0.0178	0.0000
Smoker	**0.8241**	0.1120	0.0844	**1.0000**	0.1023	0.0690	**0.6351**	0.0415	0.0266
Age at first sex < 15	**0.5856**	0.4875	0.1790	0.5984	0.2945	**0.6146**	0.5396	0.3104	**0.5658**
Oral sex	**1.0000**	0.3774	**1.0000**	0.8181	0.5373	**0.9502**	**1.0000**	0.5031	**1.0000**
Anal sex	**0.6181**	0.0000	0.4729	0.3068	0.0992	**0.5055**	0.4436	0.0257	**0.9576**
Partners 5yr +	**0.5308**	0.2581	0.1254	**0.4261**	0.4047	0.3243	**0.4856**	0.2515	0.3751
2 + partners	**0.5112**	0.0000	0.2838	0.4259	0.1761	**0.7159**	**0.5985**	0.0818	0.0757
Inconsistent condom	**0.9109**	0.6943	0.7680	**0.9569**	0.7254	0.9022	0.6757	0.7119	**0.9056**
Ever used marijuana	**0.9690**	0.1685	0.6132	**0.8917**	0.3670	0.8771	**0.8640**	0.2955	0.6426
Ever used illicit drugs	**0.3083**	0.0000	0.0451	0.0000	0.0000	0.0000	0.0727	0.0000	**0.2027**
Odds of STI	White class 1 vs white class 2 (ref) **OR=2.9 (CI 95% 1.3-27.2)**			Black class 1 vs white class 2 (ref) **OR=9.9 (CI 95% 2.1-46.3)** Black class 1 vs black class 2 (ref) OR=1.04 (CI 95% 0.51-2.1)			Hispanic class 1 vs white class 2 (ref) **OR=9.5 (CI 95% 1.8-51.3)** Hispanic class 1 vs Hispanic class 2 (ref) **OR=4.2 (CI 95% 1.4-12.8)**		

Of note, when compared to Hispanic women in class 2, class 1 had a four fold increase in their odds of STI (OR=4.2 95% CI 1.4-12.8) and had the lowest chance of reporting foreign-born head of households when compared to class 2 and 3. No other associations were found.

Within group differences were less varied among males, and no class of white or Hispanic males were at greater risk of a STI (**Table 4.3**). White males in Class 1 were most sexually risky, class 2 included a higher chance of regular alcohol use and early sexual debut, and class 3 included men with unmarried head of households. None of these classes were associated with increased odds of an STI.

Class 1 black males included a higher chance of risky sexual behaviors and low income. Black males in class 2 had head of households that were less educated and reported a higher chance of regular alcohol use. Class 3 black males reported the least risky sexual behaviors (Table 3). Young black males from class 3 had over a sixteen fold increase in their odds of STI compared to white males (OR=16.4 95% CI 3.7-72.0), but not when compared to lower risk black males in class 2 (OR=1.5 95% CI 0.4-4.8).

Hispanic males in class 1 had the highest chance of reporting low income indicators and risky sexual behaviors along with excessive alcohol and illicit drug use (**Table 4.3**). Class 2 contained males with low income indicators, but a low chance of reporting risky sexual behaviors, and class 3 included males with some risky sexual behaviors and illicit drug use. None of these classes were associated with increased odds of an STI.

Table 4.3. Latent class membership and probabilities (%) for syndemic indicators in males by race, NHANES 2011-2014. (adapted from 161)

Race	White, n=250			Black, n=234			Hispanic, n=223		
Item/Variable	Class 1 (37.97%, n=106)	Class 2 (18.84%, n=53)	Class 3 (43.19%, n=121)	Class 1 (44.47%, n=89)	Class 2 (9.62%, n=19)	Class 3 (45.90%, n=91)	Class 1 (46.50%, n=91)	Class 2 (33.58%, n=66)	Class 3 (19.93%, n=39)
5+ in house	0.2040	**0.5182**	0.1378	0.1805	**0.8488**	0.0842	0.4012	**0.5667**	0.2353
HS grad or less	**0.3368**	0.0808	0.2688	0.4894	**0.6260**	0.2029	**0.8202**	0.6793	0.1781
PIR low-income	**0.4930**	0.1527	0.2677	0.4548	0.3147	**0.5875**	**0.7003**	0.5211	0.1511
HH Country non-US	0.0000	**0.0950**	0.0174	0.0182	**0.3525**	0.0804	**0.7657**	0.7340	0.1615
HH unmarried	**0.6873**	0.1554	0.5650	0.7658	0.2652	**0.8503**	**0.5649**	0.4477	0.5614
Depressed	0.0499	**0.0866**	0.0092	0.0371	0.0000	**0.1108**	**0.0856**	0.0406	0.0191
Regular alcohol use	0.1013	**0.8595**	0.3110	0.3744	**0.9066**	0.6250	0.0548	**0.4295**	0.3617
Excessive alcohol use	**0.2319**	0.0578	0.0000	**0.1413**	0.0000	0.0233	**0.2271**	0.0000	0.0000
Smoker	**0.6181**	0.0186	0.2293	**0.8612**	0.3989	0.1971	**0.5081**	0.0576	0.3128
Age at firs sex < 15	0.5726	**0.7093**	0.1666	**0.7059**	0.6186	0.3456	0.5294	0.2666	**0.6697**
Oral sex	**0.9930**	0.2028	0.6996	**0.9254**	0.2991	0.5621	**0.8819**	0.4416	0.8232
Anal sex	**0.6191**	0.0152	0.1591	**0.3606**	0.0769	0.1775	0.5018	0.0966	**0.5719**
Partners 5yr +	0.3002	**0.3058**	0.0308	0.4687	**0.5511**	0.2626	**0.4273**	0.1935	0.1120
2 + partners	**0.6482**	0.0847	0.1000	0.6874	**0.4217**	0.2637	**0.6387**	0.0910	0.3823
Inconsistent condom	**0.8902**	0.2818	0.8109	**0.8178**	0.3726	0.7599	0.7332	0.5825	**0.9415**
Uncircumcised	0.1481	**0.1952**	0.0000	0.2004	**0.4275**	0.2516	0.6026	**0.6847**	0.4120
Ever used marijuana	**0.8941**	0.2489	0.6133	**0.9884**	0.7739	0.4511	**0.9119**	0.3304	0.8311
Ever used illicit drugs	**0.2859**	0.0000	0.0105	**0.0268**	0.0000	0.0015	**0.2579**	0.0000	0.2219
Odds of STI	White class 1 vs white class 3 (ref) OR=1.3 (CI 95% 0.2-8.1)			Black class 1 vs white class 3 (ref) **OR=16.4 (CI 95% 3.7-72.0)** Black class 1 vs black class 2 (ref) OR=1.5 (CI 95% 0.4-4.8)			Hispanic class 1 vs white class 3 (ref) OR=3.3 (CI 95% 0.62-17.3) Hispanic class 1 vs Hispanic class 2 (ref) OR=1.5 (CI 95% 0.3-6.5)		

4.4. Discussion

Improving sexual health in young adults is a public health goal [162] but interventions that are effective at reducing STIs in this group are limited [160]. There has been increasing interest in syndemic theory to provide a holistic approach to developing public health initiatives to reduce STIs [163]. The results of this study support a syndemic in young women that involves low income indicators, substance abuse and sexual behaviors that co-occur to increase risk for STI. Classes identified as high-risk for STI were characterized by substance use and depression, highlighting the importance of addressing mental health issues early in life.

Race/ethnicity and sex are crucial factors in the development and exacerbation of social disadvantage [62]. Across all racial groups, women reported a higher probability of an unmarried head of household, even among low-risk profiles. High risk profiles for Hispanic and Black women had exceedingly high rates of STIs and different patterns of risk exposure compared to high-risk profiles for white women. Similarly, the chance of reporting depression was high among all high-risk profiles stratified by race and ethnicity in women, a finding confirmed by Senn et al. when examining syndemics in patients at an urban STD clinic [164]. High risk Hispanic women were lower income and reported greater proportions of uneducated, US born and unmarried head of households. Foreign-born head of household was protective for Hispanic young women, consistent with many studies of health among Hispanic Americans, including those focusing on sexual risk behaviors and STIs [165] [166].

High-risk profiles in Black women were characterized by low income and unmarried head of households, but risk behaviors did not differ greatly compared to high risk white and Hispanic young women. Black young women in the high-risk profile reported a lower proportion of anal and oral sex than white and Hispanic high risk women, but still had the highest odds of STI, consistent with previous findings [62]. Thus, targeting specific individual sexual risk behaviors may not decrease STIs in Black women. Based on the syndemic approach, interventions for Black women must include more than behavioral risk reduction, and should focus more on environment, social engagement, and access to resources.

This study goes beyond individual STIs risk factors to classify the co-occurrence of those factors among different groups (i.e. syndemics) using a national representative sample with biological confirmed data. Syndemics have been studied in the context of substance use, violence and HIV risk behavior [159] but generalizability is an important limitation of that literature.

Some limitations persist in this analysis. More recent NHANES data (NHANES 2015-2016) was not available at the time of this analysis. The sample of "other" race groups (such as Asians) was too small for sensitivity analysis. Temporality may be an important factor in the development of syndemics, but this cannot be established using cross-sectional data. Some complexities of the sampling design of NHANES, such as a stratification and cluster variables, are not completely accounted for in the LCA procedure in SAS, although sample weights were included for this analysis. Lastly, early

and mid-adolescence are important developmental periods that need to be examined but NHANES data on STIs for participants age less than 18 are not available for public use.

4.5. Conclusion

Interventions to reduce STIs among young adults need to be culturally appropriate and tailored to specific groups. As reported in many other studies, Black women had increased risk of STIs even when reporting less risk behaviors. In contrast, high-risk men reported many risky behaviors that are the target of standard STIs prevention efforts. This suggest that traditional STI interventions focused on sexual behavior may benefit men but not women, especially minority women.

5. CONCLUSIONS

The purpose of this dissertation was to identify profiles of risk for STI's among young adults in the context of psychosocial perspectives using a syndemic framework. In the studies presented in this dissertation, syndemics were identified among a nationally representative sample of young women using a latent class analysis. Further race/ethnic analysis revealed additional syndemic indicators among young minority women.

Additionally, this dissertation also examined chlamydia associated pregnancy outcomes in a population of primarily minority pregnant women revealing differences in outcomes by maternal age. Overall, these studies contribute to the literature through utilizing LCA, a statistically informative method, to identifying syndemics among minority women and to examine potential outcomes related to STIs during pregnancy for young minority women.

Chapter 2 examined a population of primarily minority women and their risk for chlamydia associated adverse birth outcomes. Results suggested an association between *Chlamydia trachomatis* and medically indicated preterm birth among young women, but not other preterm birth subtypes. A significant relationship was found between *C. trachomatis* and term preeclampsia among Black and older women. This finding may suggest that untreated chlamydia infections may trigger global inflammatory responses eliciting preeclampsia in a later pregnancy. Although further confirmation is needed with complete previous infection history, this could be a vital support for age and race/ethnic specific screening among younger women and subsequent confirmatory test of cure. Future work should collect complete data on previous infection and test of cure to better

understand the relationship between preeclampsia and chlamydia. A racially diverse longitudinal pregnancy cohort would be beneficial in confirming these findings and best informing chlamydia prevention in pregnant women. Including more behavioral risk information would also allow the use of a syndemic approach and the development of risk profiles for a chlamydia related pregnancy outcome.

To better understand the most useful methods to identifying syndemics, a comparison of syndemic scoring analysis and LCA was conducted in Chapter 3. Results reveal that scoring analysis to determine syndemics were unable to identify specific psychosocial indicators associated with increased risk of STI, how the indicators interacted or co-occurred, nor distinguished any differences in indicators between men and women. The syndemic scoring analysis lacked useful information related to the circumstances that may increase STI risk, making it difficult to translate findings into population level interventions. In contrast, the models from the LCA provided more informative results by determining the exact indicators that co-occurred, and the prevalence of reporting those indicators among risk classes. A syndemic of depression and smoking co-occurred with sexual risk behaviors to increase the risk of STI among young women was found. Furthermore, the LCA showed distinct differences in indicators related to STI between men and women. As women were determined to have syndemic profiles, next steps will include collection of longitudinal data on early adolescence into adulthood to examine the timing and onset of syndemics in young women. This finding may better inform gender-based STI interventions.

Chapter 4 utilized LCA to classify the co-occurrence of the psychosocial syndemic factors among different race/ethnic groups, which resulted in several interesting findings. A syndemic of poverty indicators, depression, excessive alcohol use and smoking was associated with increased risk of STI in Black women, while poverty indicators, sexual risk behaviors, and illicit drug use were associated with increased odds of STI in Hispanic women. Surprisingly, despite reporting fewer risky behaviors, Black women had increased odds of STIs. LCA identified these specific issues that complicated risk of STI for Black women. These finding suggest that traditional STI interventions focused on sexual behavior may not be beneficial for women, especially minority women. Interventions to reduce STIs among young adults need to be culturally appropriate and tailored to specific groups based on population level data. Future research should examine cohorts of Black and Hispanic women and collect data on their geographic surroundings to include in their syndemic profile. Including neighborhood level data is a novel approach to better understanding the specific needs of minority women based on their surroundings and will best inform prevention activities that will be specifically tailored to them to reduce morbidity.

Some limitations must be noted from each of these analyses. In Chapter 2 and 3, examinations of NHANES data are limited in ability to establish temporality due to the cross-section design of the study. Also, data from the 2015-2016 and 2017-2018 waves were not complete or available and were not included for this analysis. Asian, multiracial, and individuals who identified as other were too small to conduct race/ethnic analysis and were not included. Although all of the complexities of the sampling design

of NHANES (i.e., stratification and cluster variables) could not be accounted for in the LCA procedure in SAS, sample weights were included for the analyses presented in Chapters 2 and 3. A limitation of the final study was that the sample analyzed was primarily Hispanic from one geographic location. Despite the findings lacking generalizability to the larger population, the results suggest further investigation into race/ethnic specific perinatal outcomes associated with C. trachomatis are needed.

Future research should address the aforementioned limitations. The studies in this dissertation found a syndemic among Hispanic and Black women, suggesting more in depth examinations of psychosocial indicators are needed. Furthermore, incorporating additional psychosocial indicators in a perinatal cohort will greatly strengthen the understanding of adverse outcomes related to chlamydia infection. Future research should examine similar psychosocial indicators among younger individuals in mid-adolescence (age 14-18), as this is important developmental period. Longitudinal evaluations should also be conducted to examine the timing of onset syndemics for young minority women.

Overall, this dissertation provides greater insight to appropriate measures to understanding the risk of STI among a prevalent population and provide valuable information for health practitioner and researchers. Using LCA to examine the syndemics of sexually transmitted infections allows for the identification of specific psychosocial indicators that increase the odds of prevalent STIs among young adults. Identifying specific chlamydia associated pregnancy outcomes may facilitate an uptake in routine STI screenings and subsequent treatment in perinatal populations. These

findings may determine appropriate measures for evaluating populations at high risk and formulate prevention strategies that are targeted, culturally appropriate, and can be evaluated for effectiveness.

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APPENDIX A

Table A. Association between *Chlamydia trachomatis* and pregnancy outcomes in singleton pregnancies for Black women N=2,971, 2011-2017

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥] RR (CI 95%)	Model 2 [β] RR (CI 95%)	Model 3[±] RR (CI 95%)
			GA at delivery		
Term ≥ 37 weeks (ref)	2441 (88.1%)	178 (88.6%)	--	--	--
Preterm < 37 weeks	329 (11.9%)	23 (11.4%)	0.96 (0.65-1.43)	1.08 (0.65-1.78)	1.06 (0.65-1.75)
Indicated PTB	129 (5.0%)	14 (7.2%)	1.46 (0.86-2.48)	1.77 (0.90-3.49)	1.72 (0.87-3.43)
Spontaneous PTB	89 (3.5%)	4 (2.2%)	0.63 (0.23-1.69)	0.76 (0.24-2.37)	0.73 (0.23-2.28)
			Preeclampsia (PE)		
Normotensive (ref)	2251 (91.4%)	155 (87.6%)	--	--	--
Overall PE	213 (8.6%)	22 (9.4%)	1.44 (0.95-2.17)	**1.83 (1.17-2.88)**	**1.76 (1.12-2.75)**
Term PE	84 (3.6%)	12 (7.2%)	**2.0 (1.11-3.58)**	**2.50 (1.23-5.06)**	**2.46 (1.21-4.98)**
Preterm PE	129 (5.4%)	10 (6.1%)	1.12 (0.60-2.09)	1.60 (0.85-3.01)	1.50 (0.80-2.83)
			Chorioamnionitis		
No (ref)	2588 (94.4%)	184 (93.4%)	--	--	--
Yes	153 (5.6%)	13 (6.6%)	1.18 (0.68-2.04)	1.24 (0.66-2.35)	1.28 (0.68-2.41)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX B

Table B. Association between *Chlamydia trachomatis* and pregnancy outcomes in singleton pregnancies for White women N=3959, 2011-2017

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
			RR (CI 95%)	RR (CI 95%)	RR (CI 95%)
			GA at delivery		
Term ≥ 37 weeks (ref)	3628 (96.7%)	36 (80.0%)	--	--	--
Preterm < 37 weeks	286 (7.3%)	9 (20%)	**2.74 (1.51-4.96)**	**2.40 (1.10-5.23)**	**2.30 (1.06-5.01)**
Indicated PTB	117 (3.1%)	5 (11.9%)	**3.81 (1.64-8.84)**	2.91 (0.98-8.60)	2.90 (0.97-8.66)
Spontaneous PTB	77 (2.1%)	2 (5.1%)	2.47 (0.63-9.69)	3.24 (0.76-13.9)	3.12 (0.71-13.8)
			Preeclampsia (PE)		
Normotensive (ref)	3456 (95.9%)	39 (97.5%)	--	--	--
Overall PE	147 (4.1%)	1 (2.5%)	0.61 (0.09-4.27)	*	*
Term PE	66 (1.9%)	0 (0%)	*	*	*
Preterm PE	81 (2.3%)	1 (2.5%)	1.09 (0.16-7.65)	*	*
			Chorioamnionitis		
No (ref)	3743 (96.2%)	43 (97.7%)	--	--	--
Yes	148 (3.8%)	1 (2.3%)	0.60 (0.09-4.17)	0.55 (0.08-3.84)	0.55 (0.08-3.54)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

Relative risk was not calculated due to small sample size

[¥]*Unadjusted estimates*

[β] Estimates were adjusted for maternal age, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX C

Table C. Association between *Chlamydia trachomatis* and pregnancy outcomes in singleton pregnancies for Hispanic women N=14,213, 2011-2017

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
			RR (CI 95%)	RR (CI 95%)	RR (CI 95%)
			GA at delivery		
Term ≥ 37 weeks (ref)	12226 (90.4%)	627 (90.5%)	--	--	--
Preterm < 37 weeks	1294 (9.6%)	66 (9.5%)	0.99 (0.79-1.26)	0.97 (0.72-1.32)	0.96 (0.71-1.31)
Indicated PTB	403 (3.2%)	25 (3.8%)	1.21 (0.81-1.79)	1.23 (0.74-2.05)	1.23 (0.73-2.06)
Spontaneous PTB	515 (4.0%)	24 (3.7%)	0.92 (0.61-1.37)	0.76 (0.44-1.31)	0.74 (0.43-1.28)
			Preeclampsia (PE)		
Normotensive (ref)	11376 (92.1%)	579 (91.5%)	--	--	--
Overall PE	976 (7.9%)	54 (8.5%)	1.08 (0.83-1.40)	1.13 (0.84-1.53)	1.08 (0.80-1.47)
Term PE	507 (4.3%)	38 (6.2%)	**1.44 (1.05-1.99)**	**1.44 (1.01-2.06)**	1.39 (0.97-2.00)
Preterm PE	469 (4.0%)	16 (2.7%)	0.68 (0.42-1.11)	0.72 (0.40-1.30)	0.67 (0.37-1.22)
			Chorioamnionitis		
No (ref)	2588 (94.4%)	184 (93.4%)	--	--	--
Yes	153 (5.6%)	13 (6.6%)	1.30 (1.00-1.70)	1.21 (0.90-1.63)	1.20 (0.88-1.63)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX D

Table D. *Chlamydia trachomatis* infections among foreign born vs US born women and complications n=13,118, 2011-2017

Variable	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
		GA at delivery		
Term ≥ 37 weeks (ref)	481 (90.2%)	--	--	--
Preterm <37 weeks	52 (9.8%)	1.06 (0.81-1.38)	0.96 (0.68-1.35)	0.91 (0.64-1.29)
Indicated PTB	18 (3.6%)	1.25 (0.79-2.00)	1.10 (0.57-2.04)	1.02 (0.54-1.90)
Spontaneous PTB	20 (4.0%)	1.04 (0.67-1.62)	0.82 (0.45-1.48)	0.76 (0.42-1.39)
		Preeclampsia (PE)		
Normotensive (ref)	449 (91.6%)	--	--	--
Overall PE	41 (8.7%)	1.09 (0.81-1.48)	1.12 (0.80-1.57)	1.04 (0.74-1.46)
Term PE	28 (5.9%)	1.40 (0.97-2.03)	1.36 (0.90-2.05)	1.30 (0.86-1.98)
Preterm PE	13 (2.8%)	0.75 (0.44-1.29)	0.77 (0.40-1.48)	0.68 (0.35-1.31)
		Chorioamnionitis		
No (ref)	491 (92.8%)	--	--	--
Yes	38 (7.2%)	1.21 (0.88-1.65)	1.20 (0.86-1.67)	1.22 (0.87-1.71)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk
*Relative risk was not calculated due to small sample size
[¥]Unadjusted estimates
[β] Estimates were adjusted for maternal age, race, marital status, education, insurance type, alcohol and gestational age at first prenatal visit
[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX E

Table E. Association between *Chlamydia trachomatis* and pregnancy outcomes among singleton nulliparous pregnancies N=5944, 2011-2017

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
			RR (CI 95%)	RR (CI 95%)	RR (CI 95%)
			GA at delivery		
Term ≥ 37 weeks (ref)	5146 (91.5%)	295 (91.6%)	**--**	**--**	--
Preterm < 37 weeks	476 (8.5%)	27 (8.4%)	0.99 (0.68-1.43)	1.06 (0.67-1.67)	1.06 (0.67-1.66)
Indicated PTB	128 (2.4%)	12 (3.9%)	1.62 (0.91-2.89)	**2.46 (1.26-4.83)**	**2.46 (1.25-4.85)**
Spontaneous PTB	152 (2.8%)	9 (2.9%)	1.04 (0.53-2.01)	0.46 (0.15-1.45)	0.44 (0.14-1.38)
			Preeclampsia (PE)		
Normotensive (ref)	4528 (90.5%)	240 (85.4%)	--	--	--
Overall PE	478 (9.6%)	41 (14.6%)	**1.53 (1.14-2.05)**	**1.48 (1.06-2.07)**	**1.43 (1.02-2.00)**
Term PE	198 (4.2%)	15 (5.9%)	**1.68 (1.14-2.46)**	1.43 (0.92-2.23)	1.41 (0.89-2.22)
Preterm PE	280 (5.8%)	26 (9.8%)	1.40 (0.84-2.34)	1.71 (0.98-2.99)	1.59 (0.91-2.78)
			Chorioamnionitis		
No (ref)	4950 (88.7)	274 (85.9%)	--	--	--
Yes	634 (11.3%)	45 (14.1%)	1.24 (0.94-1.64)	1.24 (0.91-1.70)	1.22 (0.88-1.68)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, race, foreign born status, marital status, education, insurance type, alcohol and gestational age at first prenatal visit

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX F

Table F. Pregnancy outcomes and complications with Chlamydia trachomatis infections among women who initiated care in the first trimester 2011-2017, n=11040

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
		GA at delivery			
Term ≥ 37 weeks (ref)	8460 (79.1%)	273 (80.3%)	--	--	--
Preterm <37 weeks	2240 (20.9%)	67 19.7%)	0.91 (0.63-1.31)	0.89 (0.58-1.35)	0.87 (0.57-1.34)
		Preterm Birth Subtypes			
Term Births (ref)	9793 (96.5%)	313 (95.1%)	--	--	--
Indicated PTB	350 (4.5%)	16 (4.9%)	1.41 (0.86-2.30)	1.51 (0.87-2.63)	1.49 (0.85-2.61)
Spontaneous PTB	311 (3.1%)	7 (2.2%)	0.71 (0.34-1.49)	0.59 (0.24-1.42)	0.57 (0.23-1.38)
		Preeclampsia and subtypes			
Preeclampsia (PE)	9092 (93.0%)	272 (89.8%)	--	--	--
Overall PE	680 (7.0%)	31 (10.2%)	**1.47 (1.04-2.07)**	1.27 (0.89-1.80)	1.23 (0.86-1.75)
Term PE	322 (3.4%)	19 (6.5%)	**1.91 (1.22-2.99)**	**1.61 (1.02-2.52)**	**1.59 (1.01-2.51)**
Preterm PE	358 (3.8%)	12 (4.2%)	1.15 (0.63-1.96)	0.94 (0.51-1.74)	0.88 (0.47-1.62)
		Chorioamnionitis			
No (ref)	10025 (94.4%)	309 (91.7%)	--	--	--
Yes	589 (5.6%)	28 (8.3%))	**1.50 (1.04-2.15)**	1.28 (0.88-1.87)	1.33 (0.91-1.94)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*****Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, race, marital status, education, insurance type, and alcohol

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX G

Table G. Pregnancy outcomes and complications with *Chlamydia trachomatis* infections among women who initiated care in the second trimester 2011-2017, n=7285

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
		GA at delivery			
Term ≥ 37 weeks (ref)	5438 (79.2%)	326 (7.2%)	--	--	--
Preterm <37 weeks	1425 (20.8%)	96 (22.8%)	1.26 (0.96-1.66)	1.28 (0.94-1.73)	1.27 (0.93-1.73)
		Preterm Birth Subtypes			
Term Births (ref)	6262 (96.9%)	374(95.4%)	--	--	--
Indicated PTB	202 (3.1%)	18 (4.6%)	1.47 (0.92-2.35)	**1.79 (1.06-3.01)**	**1.74 (1.03-2.95)**
Spontaneous PTB	228 (3.5%)	18 (4.6%)	1.31 (0.82-2.09)	1.12 (0.65-1.92)	1.07 (0.62-1.84)
		Preeclampsia and subtypes			
None (ref)	5841 (93.2%)	357 (91.8%)	--	--	--
Overall PE	429 (6.8%)	32 (8.2%)	1.20 (0.85-1.70)	1.20 (0.83-1.73)	1.13 (0.78-1.63)
Term PE	219 (6.1%)	22 (5.8%)	**1.61 (1.05-2.46)**	1.46 (0.92-2.29)	1.40 (0.89-2.21)
Preterm PE	210 (3.5%)	10 (2.7%)			
		Chorioamnionitis			
No (ref)	6425 (94.5%)	387 (92.8%)	--	--	--
Yes	375 (5.5%)	30 (7.2%)	1.30 (0.91-1.87)	1.02 (0.69-1.50)	1.05 (0.71-1.57)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*****Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, race, marital status, education, insurance type, and alcohol

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX H

Table H. Pregnancy outcomes and complications with *Chlamydia trachomatis* infections among women who initiated care in the third trimester 2011-2017, n=1543

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
			GA at delivery		
Term ≥37 weeks (ref)	1176 (81.2%)	71 (74.7%)	--	--	--
Preterm <37 weeks	272 (18.8%)	24 (25.3%)	1.24 (0.62-2.48)	1.52 (0.67-3.45)	1.53 (0.68-3.44)
			Preterm Birth Subtypes		
Term Births (ref)	1351 (98.5%)	88 (96.7%)	--	--	--
Indicated PTB	20 (1.5%)	3 (3.3%)	2.26 (0.68-7.46)	1.84 (0.40-8.42)	1.81 (0.39-8.27)
Spontaneous PTB	48 (3.4%)	3 (3.3%)	0.96 (0.30-3.02)	1.04 (0.25-4.34)	1.05 (0.25-4.41)
			Preeclampsia and subtypes		
None (ref)	1245 (94.5%)	75 (91.5%)	--	--	--
Overall PE	73 (5.5%)	7 (8.5%)	1.54 (0.73-3.24)	1.33 (0.53-3.32)	1.29 (0.52-3.22)
Term PE	46 (3.6%)	3 (3.8%)	1.08 (0.34-3.39)	0.78 (0.18-3.29)	0.78 (0.18-3.30)
Preterm PE	27 (2.1%)	4 (5.1%)	2.38 (0.86-6.65)	2.60 (0.76-8.86)	2.39 (0.70-8.22)
			Chorioamnionitis		
No (ref)	1347 (93.8%)	88 (92.6%)	--	--	--
Yes	89 (6.2%)	7 (7.4%)	1.19 (0.57-2.49)	1.20 (0.58-2.47)	1.05 (0.48-2.30)

Modified Poisson regression with robust error measurements were used to calculate unadjusted relative risk

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, race, marital status, education, insurance type, and alcohol

[±]Model 2 adjustments plus maternal comorbidities and co-infections with other STIs

APPENDIX I

Table I. Pregnancy outcomes and complications with *Chlamydia trachomatis* infections among women who initiated care in the third trimester 2011-2017, n=1543

Variable	CT negative n (%)	CT positive n (%)	Model 1[¥]	Model 2 [β]	Model 3[±]
		GA at delivery			
Term ≥37 weeks (ref)	1176 (81.2%)	71 (74.7%)	--	--	--
Preterm <37 weeks	272 (18.8%)	24 (25.3%)	1.34 (0.94-1.93)	**1.44 (1.00-2.08)**	1.31 (0.82-2.16)
		Preterm Birth Subtypes			
Term Births (ref)	1351 (98.5%)	88 (96.7%)	--	--	--
Indicated PTB	20 (1.5%)	3 (3.3%)	2.26 (0.68-7.46)	1.99 (0.56-7.06)	*
Spontaneous PTB	48 (3.4%)	3 (3.3%)	0.96 (0.30-3.02)	*	*
		Preeclampsia and subtypes			
None (ref)	1245 (94.5%)	75 (91.5%)	--	--	--
Overall PE	73 (5.5%)	7 (8.5%)	1.54 (0.73-3.24)	1.65 (0.77-3.54)	*
Term PE	46 (3.6%)	3 (3.8%)	1.08 (0.34-3.39)	1.08 (0.34-3.43)	*
Preterm PE	27 (2.1%)	4 (5.1%)	2.38 (0.86-6.65)	2.77 (0.97-7.87)	*

*Relative risk was not calculated due to small sample size

[¥]Unadjusted estimates

[β] Estimates were adjusted for maternal age, race, marital status, alcohol and tobacco use

[±]Model 2 adjustments plus maternal comorbidities, HIV, Gonorrhea, and Bacterial vaginosis